An Information-Theoretic Approach to Methylation Data Analysis

John Goutsias

Whitaker Biomedical Engineering Institute
The Johns Hopkins University
Baltimore, MD 21218

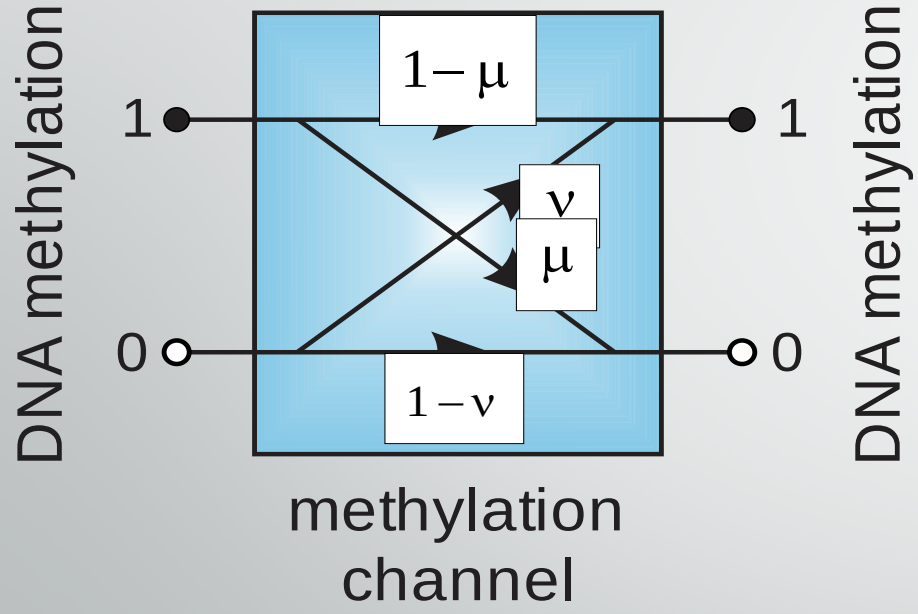
Objective

- Present an information-theoretic approach to methylation data analysis.
- This leads to:
  - Employing the Shannon entropy to quantify epigenetic stochasticity.
  - Predicting large-scale chromatin organization (compartments A/B).
  - Predicting smaller-scale chromatin organization (TADs).
  - Using an information-theoretic distance to quantify epigenetic discordance.
  - Developing a sensitivity analysis approach to quantify environmental influences on epigenetic stochasticity.

Methylation Maintenance

μ : demethylation probability

ν : methylation probability



$$P_{out}(0) = (1-\nu)P_{in}(0) + \mu P_{in}(1)$$
$$P_{out}(1) = \nu P_{in}(0) + (1-\mu)P_{in}(1)$$

Methylation Maintenance

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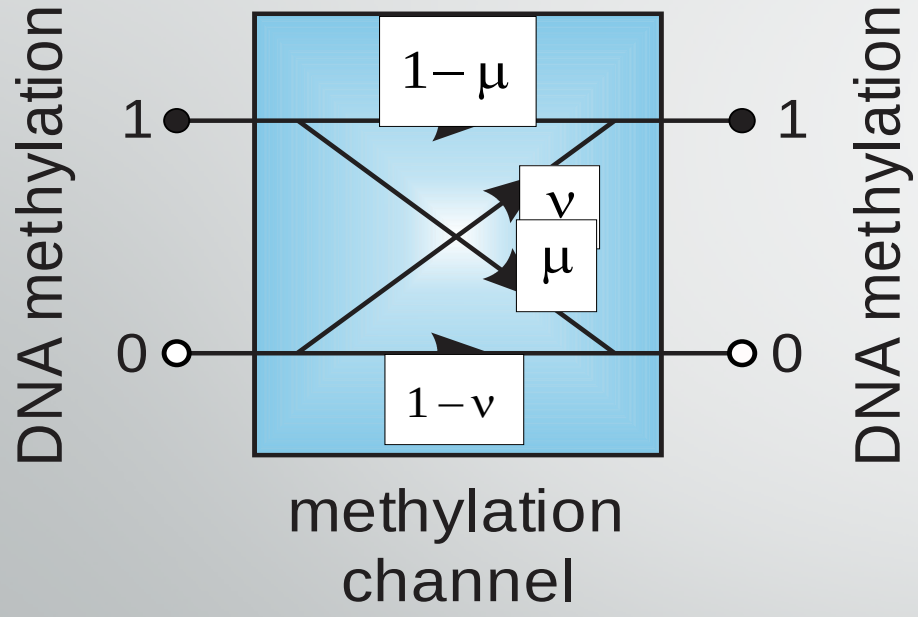


$$P_{out}(0) = (1-\nu)P_{in}(0) + \mu P_{in}(1)$$
$$P_{out}(1) = \nu P_{in}(0) + (1-\mu)P_{in}(1)$$

- Use **methylation channels** at each CpG site (noisy binary communication channels).
- Must estimate probabilities μ and ν from data
- Not possible !
- At steady-state, $P_{out} = P_{in}$ and

$$\lambda = \frac{\nu}{\mu} = \frac{P_{in}(1)}{1-P_{in}(1)}$$

Information Capacity of a Methylation Channel

- Maximum average information that can be conveyed during a maintenance step:

$$C = \max_{P(1)} \{ I(X_{out}, X_{in}) \}$$

mutual information

- **Mutual information:** a measure of mutual dependence between input and output methylation.
- Available formula for capacity, but depends on probabilities μ and ν.
- Approximate formula can be derived that depends **only** on $\lambda = \nu / \mu$.

Probability of Transmission Error

$$\pi = \Pr[\text{output methylation} \neq \text{input methylation}]$$

- Quantifies fidelity of methylation transmission through a methylation channel.
- Depends on probabilities μ and ν.
- An approximate formula can be derived that depend **only** on $\lambda = \nu / \mu$.

Energy Dissipation

- Correct transmission of the methylation state requires work.
- This consumes free energy that is dissipated to the surroundings in the form of heat.
- The minimum dissipated energy is related (for some systems) to the probability of error

$$E \sim k_B T \ln \pi$$

- **Relative dissipated energy:**

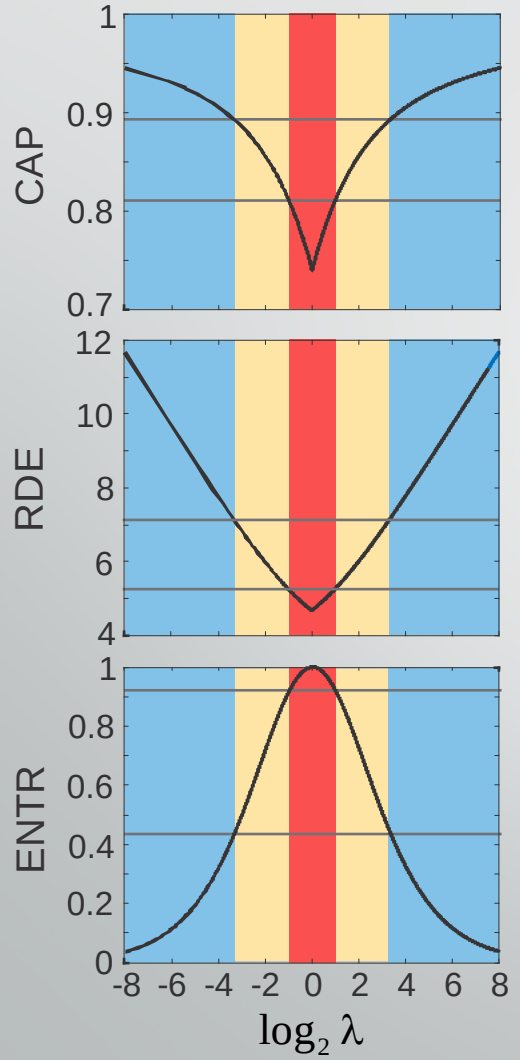
$$\varepsilon - \frac{E}{E_{max}} = -\log_2 \pi$$

Methylation Stochasticity

- We can characterize methylation stochasticity at a CpG site using the **Shannon entropy:**

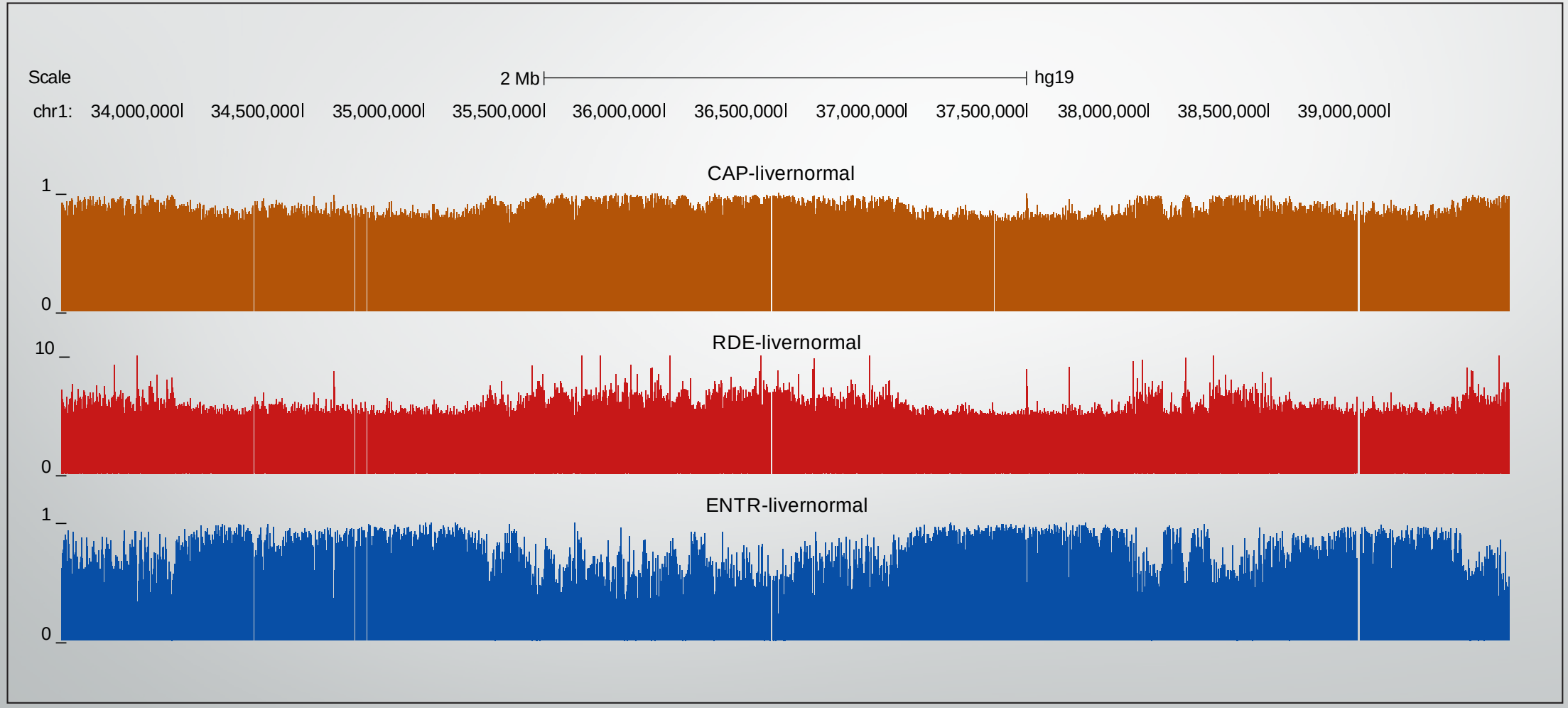
$$S = -P(0)\log_2 P(0) - P(1)\log_2 P(1)$$

Capacity, Relative Dissipated Energy, Entropy

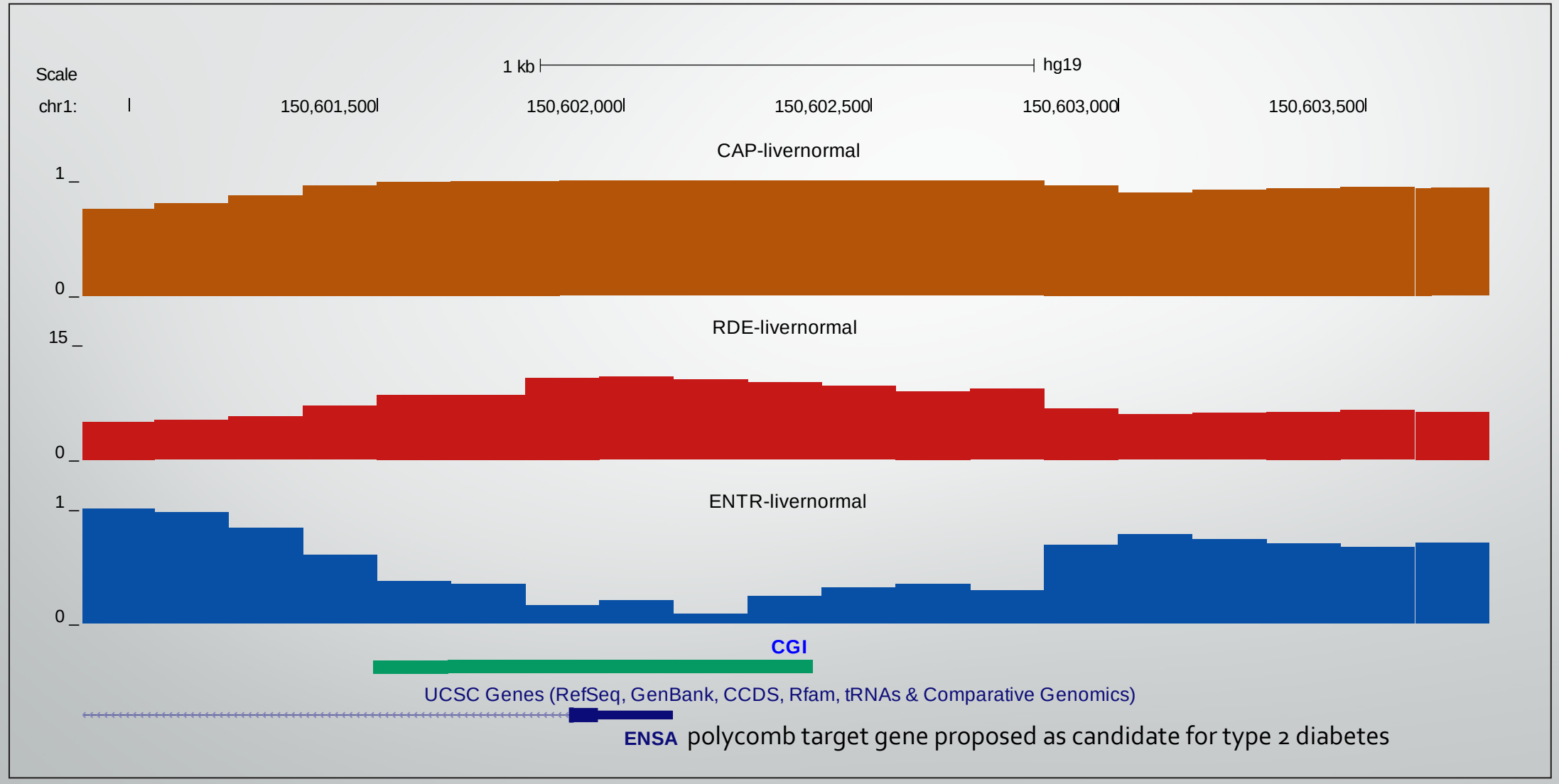


- **Reliable transmission** of methylation information within critical regions of the genome is facilitated by **high capacity** methylation channels that result in **low methylation stochasticity** at the cost of **high energy consumption**.
- **Unreliable methylation transmission** within other regions of the genome due to **low capacity** methylation channels that **consume less energy** but produce **higher levels of methylation stochasticity**.

Capacity, Relative Dissipated Energy, Entropy

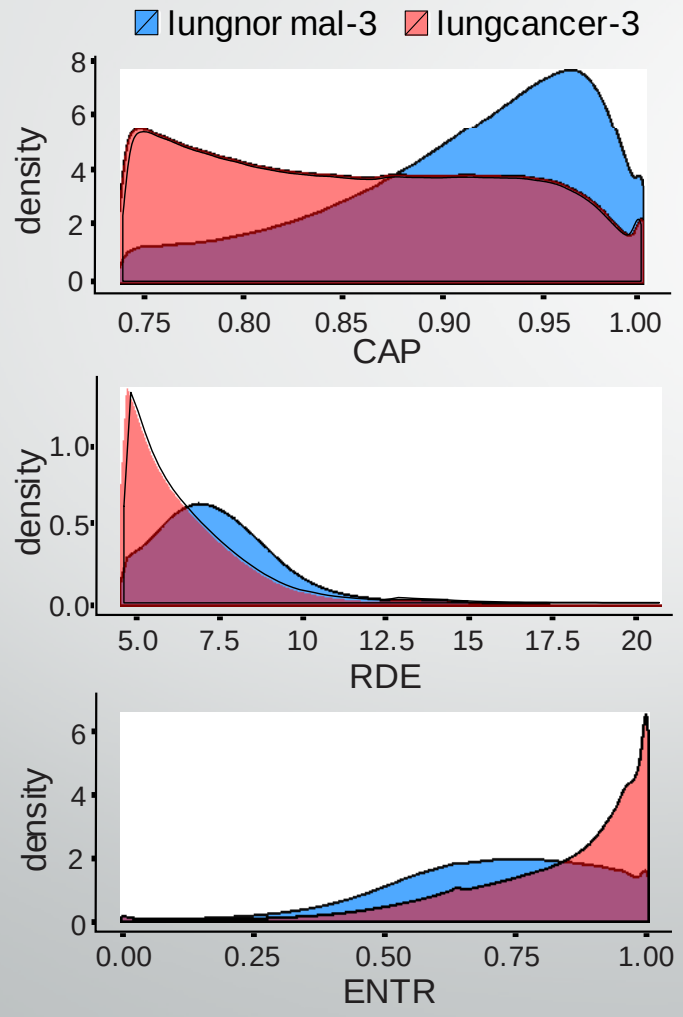


Capacity, Relative Dissipated Energy, Entropy

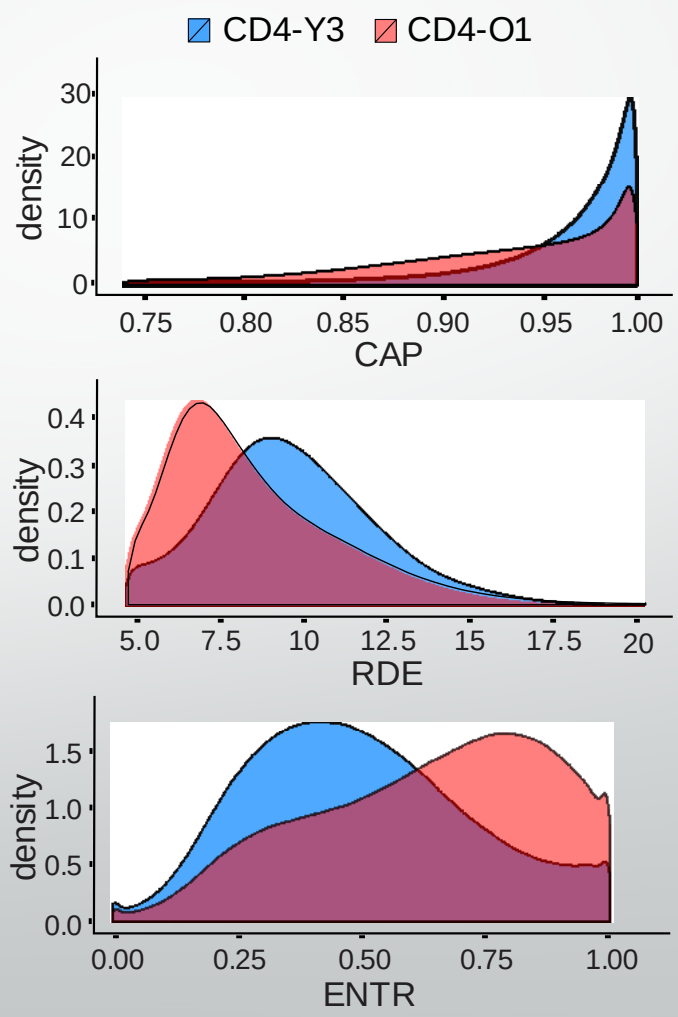


Capacity, Relative Dissipated Energy, Entropy

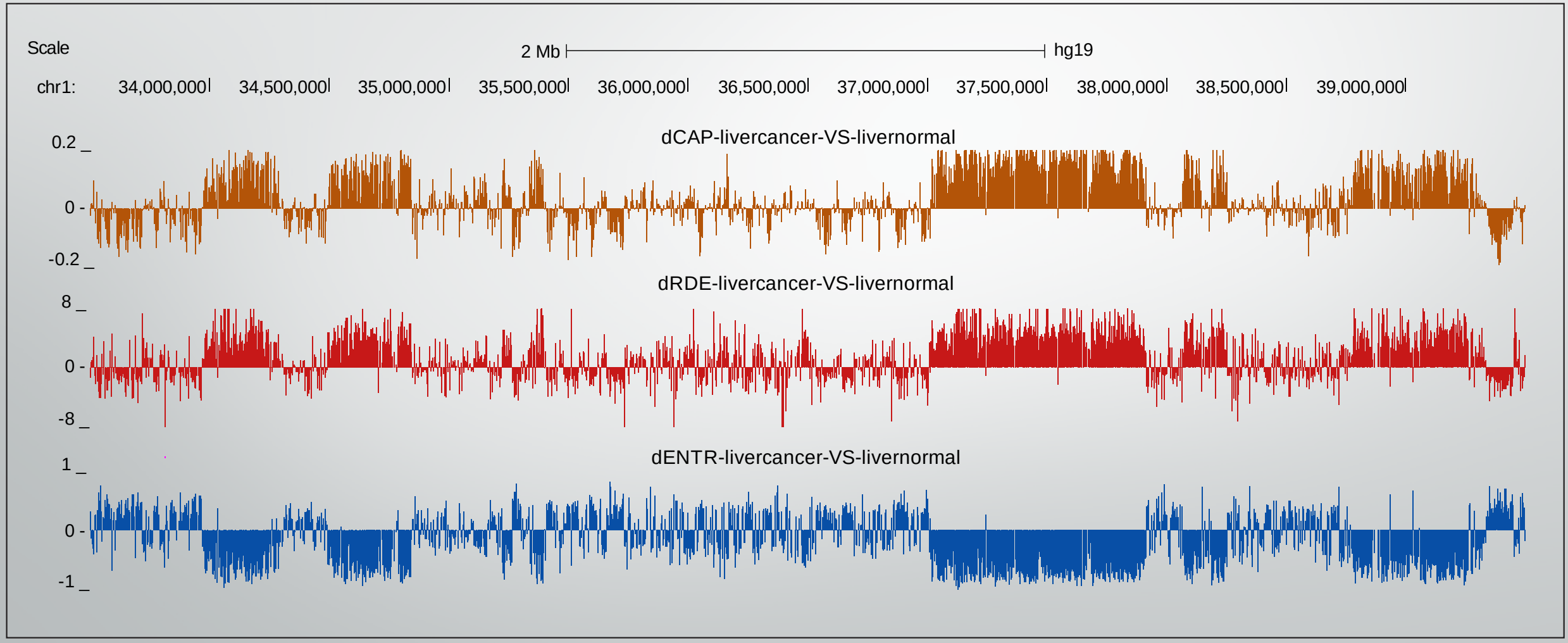
NORMAL/CANCER



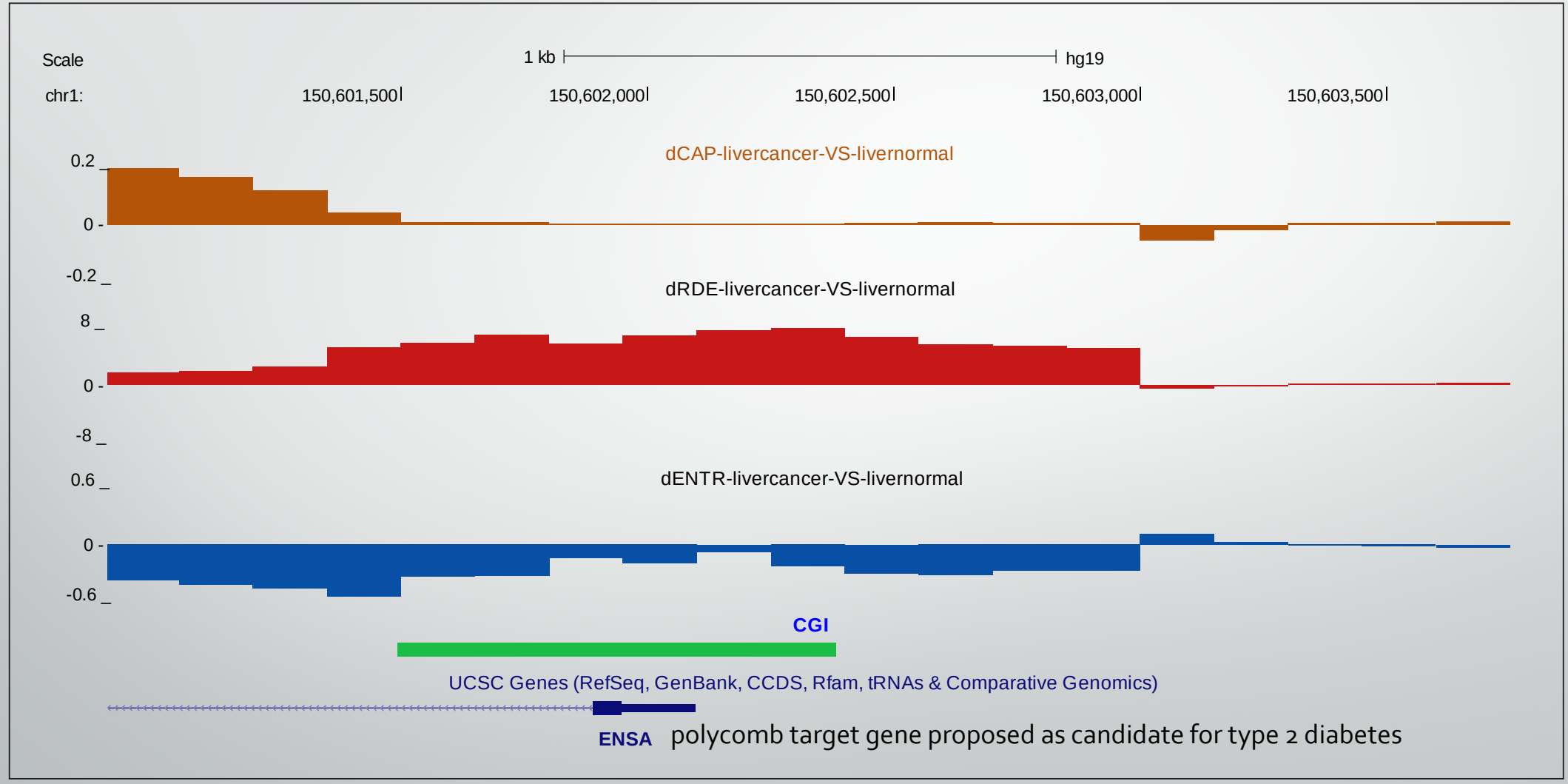
YOUNG/OLD



Capacity, Relative Dissipated Energy, Entropy



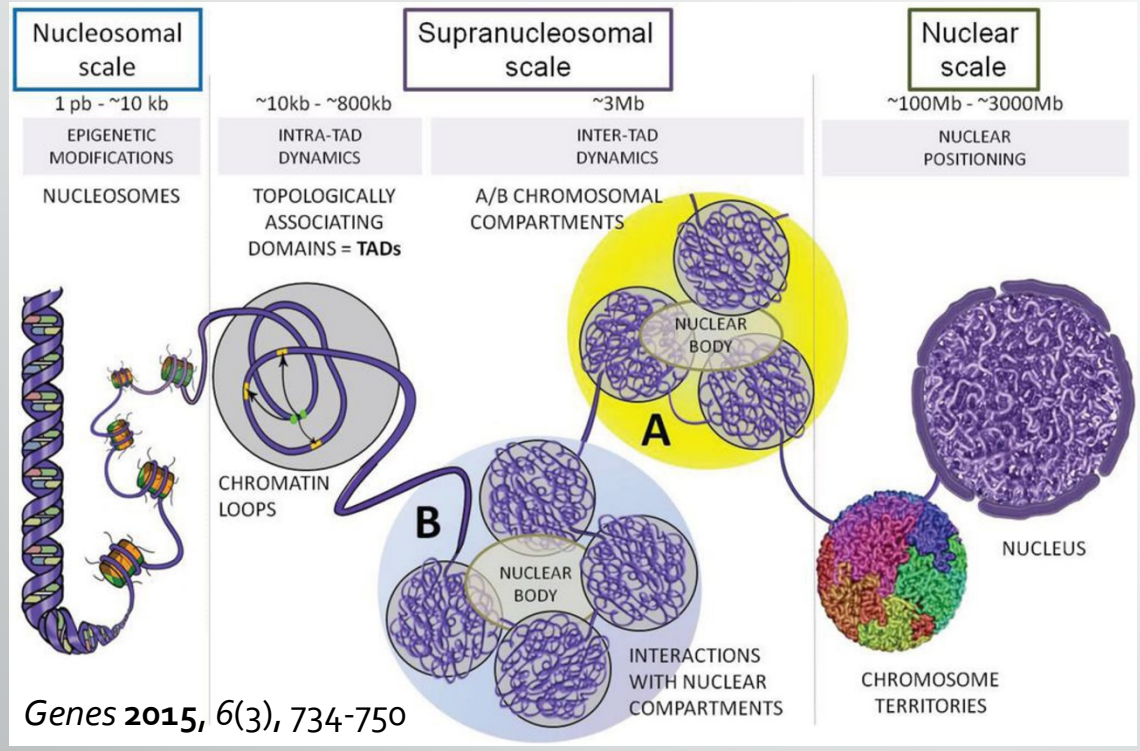
Capacity, Relative Dissipated Energy, Entropy

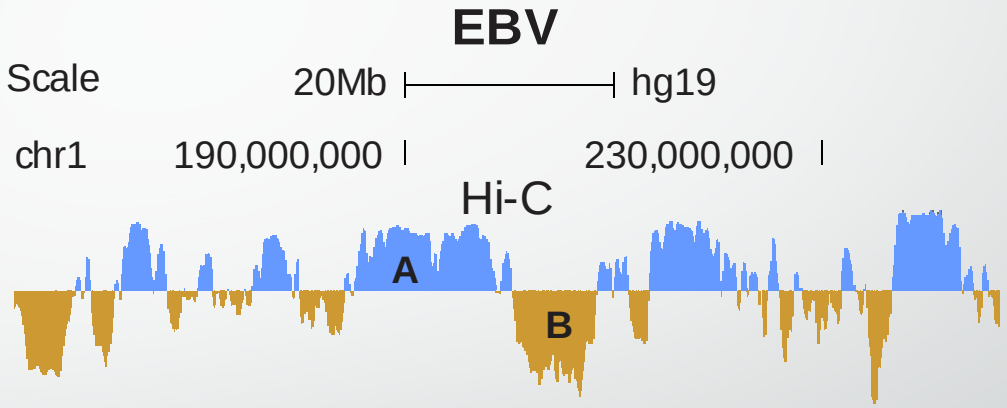


polycomb target gene proposed as candidate for type 2 diabetes

Information-Theoretic Prediction of Chromatin Organization

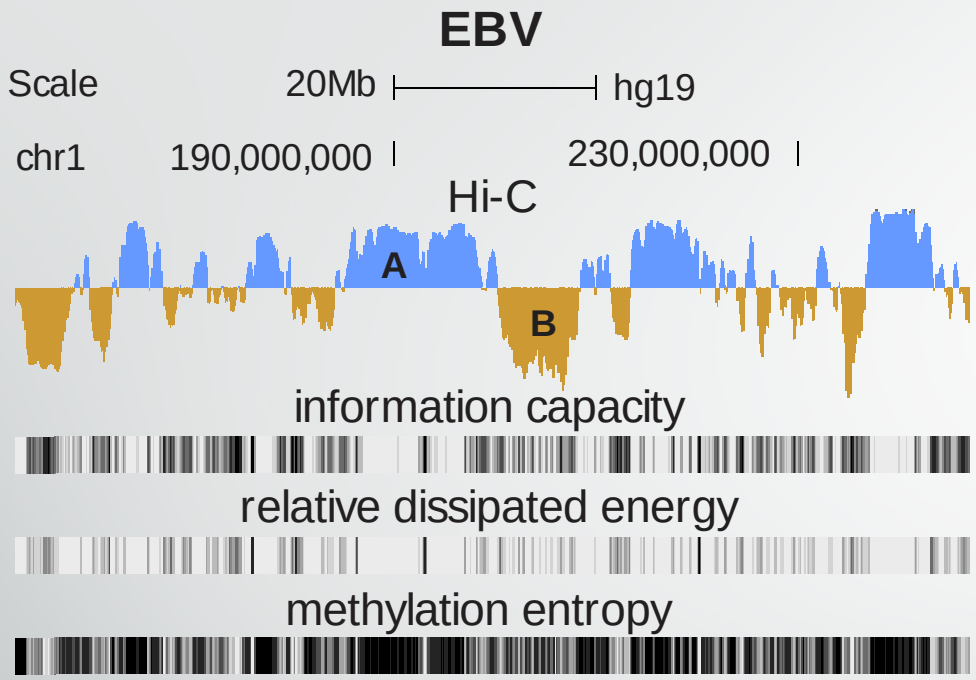
- Chromatin is organized in cell-type specific compartments A and B.

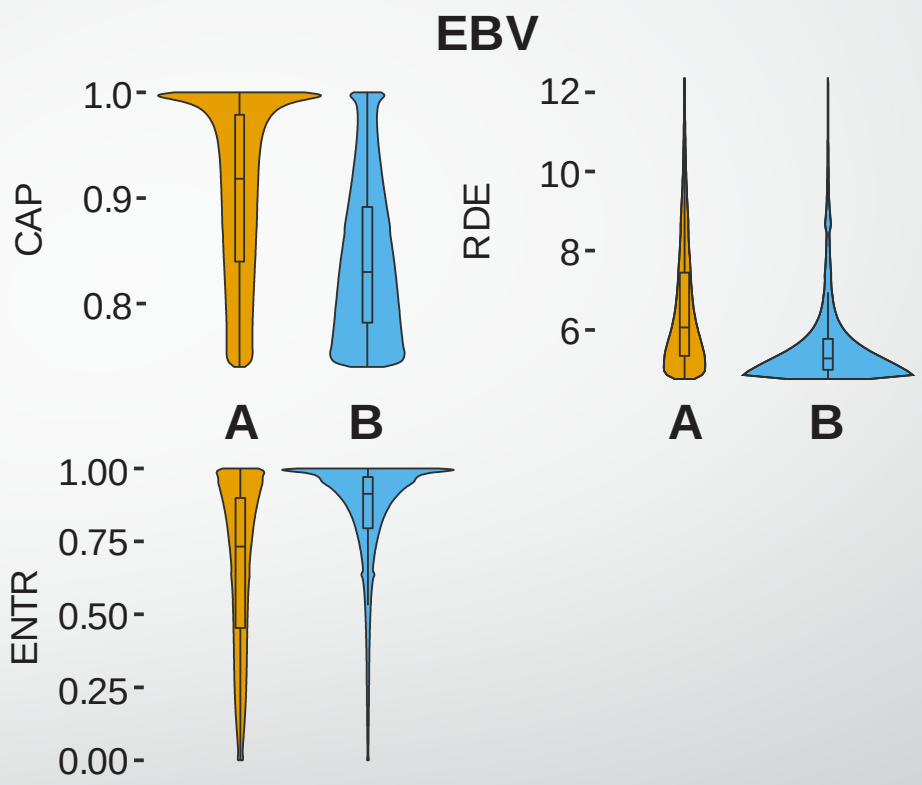




- **Compartment A**: associated with gene-rich transcriptionally active open chromatin.
- **Compartment B**: associated with gene-poor transcriptionally inactive chromatin.

Information-Theoretic Prediction of Chromatin Organization





- Enrichment of **low information capacity**, **low relative dissipated energy**, and **high entropy** within compartment B !
- Opposite true for compartment A !

Information-Theoretic Prediction of Chromatin Organization

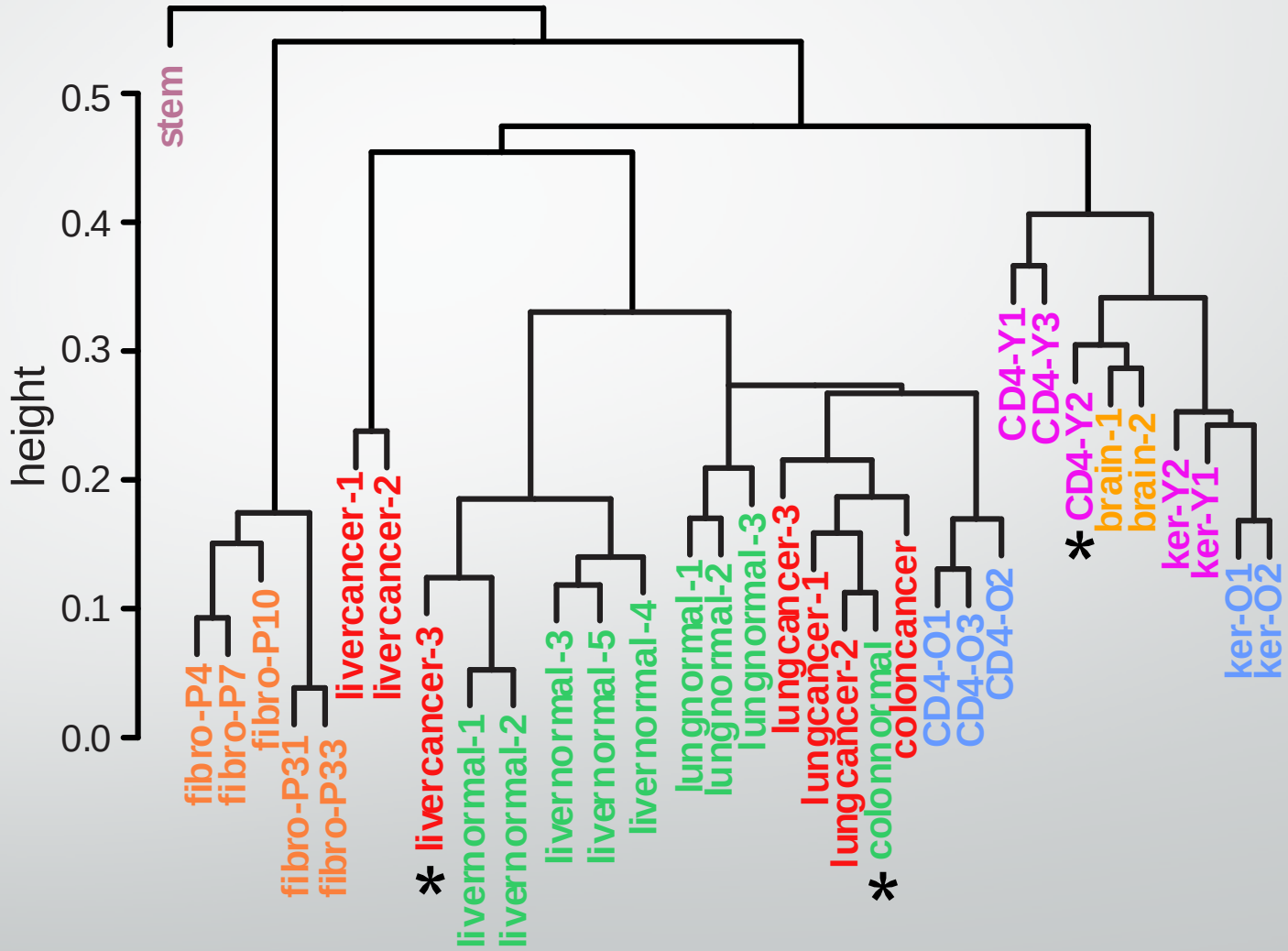
- **Random forest regression**, using information-theoretic quantities as features, learns the informational structure of compartments A/B from available "ground-truth" data.

- Achieves reliable prediction: 0.82 cross-validated average correlation and 91% average agreement between predicted and "true" A/B signals.

- **A small number of local information-theoretic properties of methylation maintenance can be highly predictive of large-scale chromatin organization !**

Information-Theoretic Prediction of Chromatin Organization

- Clustered 34 samples using the net percentage of A/B switching as a dissimilarity measure.
- 31/34 samples grouped in a biologically meaningful manner !



Quantifying Epigenetic Stochasticity

- Source of epigenetic stochasticity: Transmission of epigenetic information during maintenance through low capacity methylation channels that consume low levels of free energy.
- Quantify epigenetic stochasticity using the concept of **Shannon entropy**.
- To account for methylation dependence within a genomic region, must consider the ***joint*** Shannon entropy

$$H(X_1, X_2, \ldots, X_N) = -\sum_{x_1, x_2, \ldots, x_N} p(x_1, x_2, \ldots, x_N) \log_2 p(x_1, x_2, \ldots, x_N)$$

$$X_n = \begin{cases} 1, & n\text{-th CpG site is methylated} \\ 0, & n\text{-th CpG site is unmethylated} \end{cases}$$

- Note that

$$H(X_1, X_2, \ldots, X_N) \leq H(X_1) + H(X_2) + \cdots + H(X_N)$$

Methylation Level

- Partition the genome into non-overlapping **genomic units** of 150 bp each (determines resolution of analysis).
- Instead of focusing on **methylation patterns** within a genomic unit, we quantify methylation using the **methylation level**

$$L = \frac{1}{N}\sum_{n=1}^{N} X_n$$

$$X_n = \begin{cases} 1, & n\text{-th CpG site is methylated} \\ 0, & n\text{-th CpG site is unmethylated} \end{cases}$$

- Compute the probability distribution $P(l)$ of the methylation level from the Ising model.

Mean Methylation Level

- The **mean methylation level** (MML) is the average of the methylation means at the CpG sites within a genomic unit

$$\mathrm{E}[L] = \frac{1}{N}\sum_{n-1}^{N}\mathrm{E}[X_n]$$

Normalized Methylation Entropy

- Quantify epigenetic stochasticity within each genomic unit using the **normalized methylation entropy** (NME)

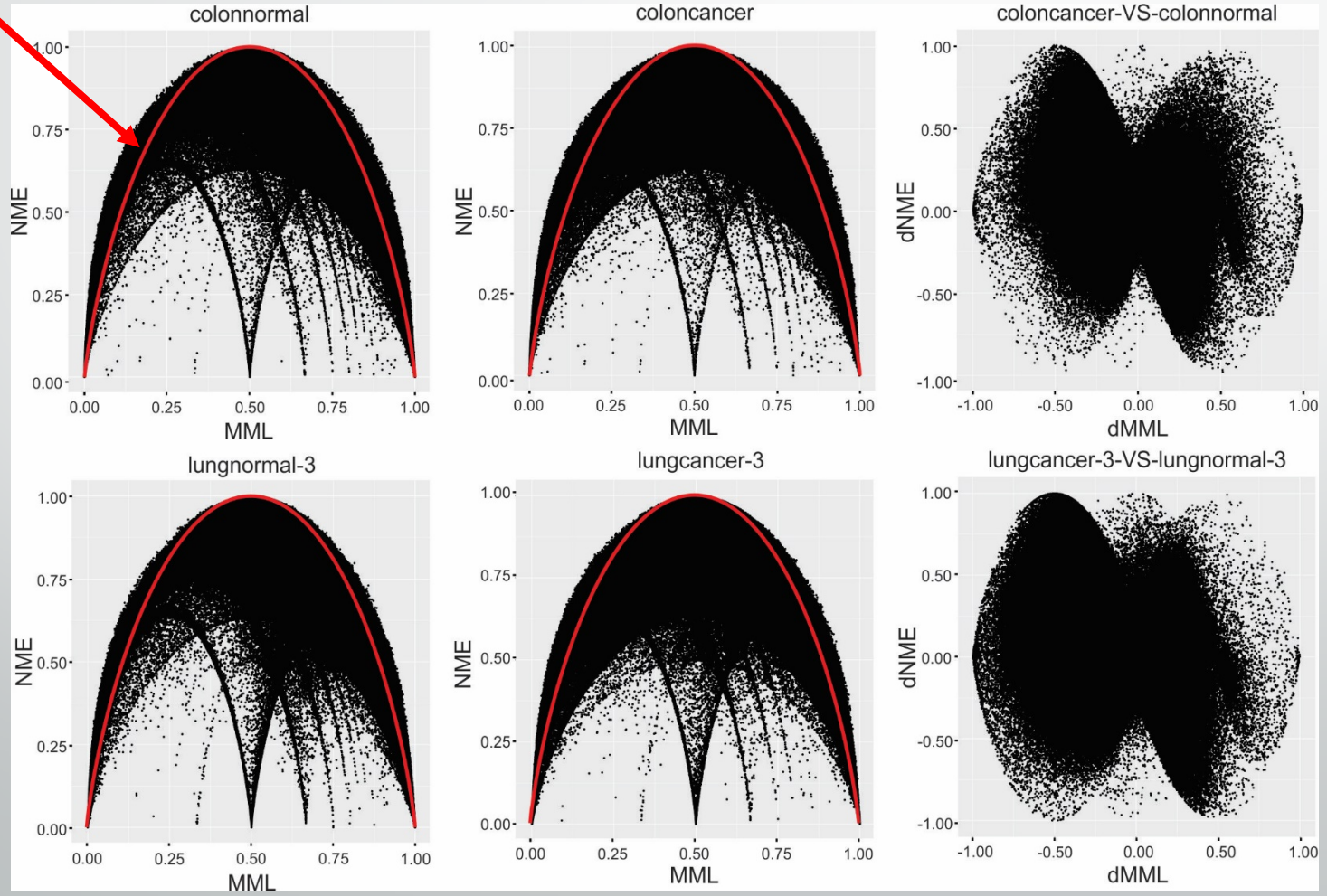
$$h = -\frac{1}{\log_2(N+1)} \sum_l P(l) \log_2 P(l)$$

- Ranges between 0 and 1
  - 0: fully ordered state
  - 1: fully disordered state

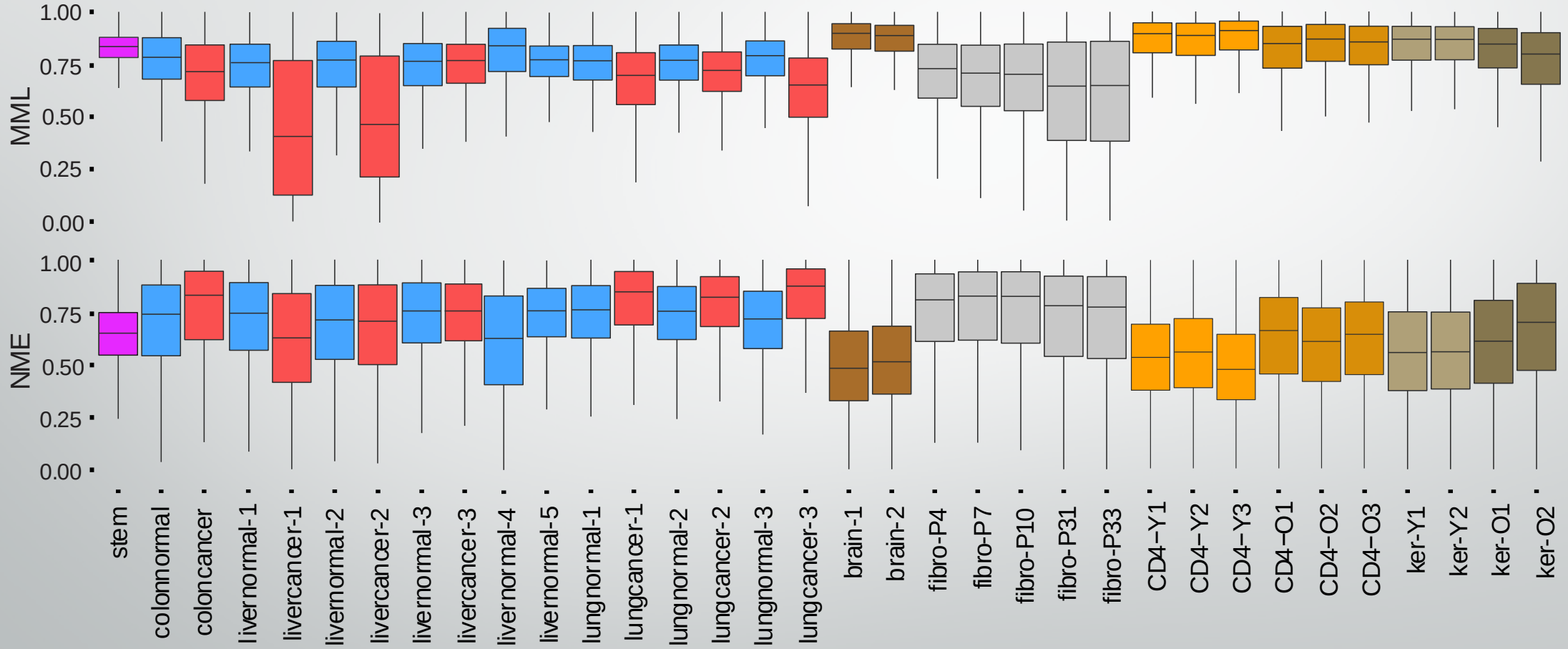
Normalized Methylation Entropy

MML not predictive of NME !

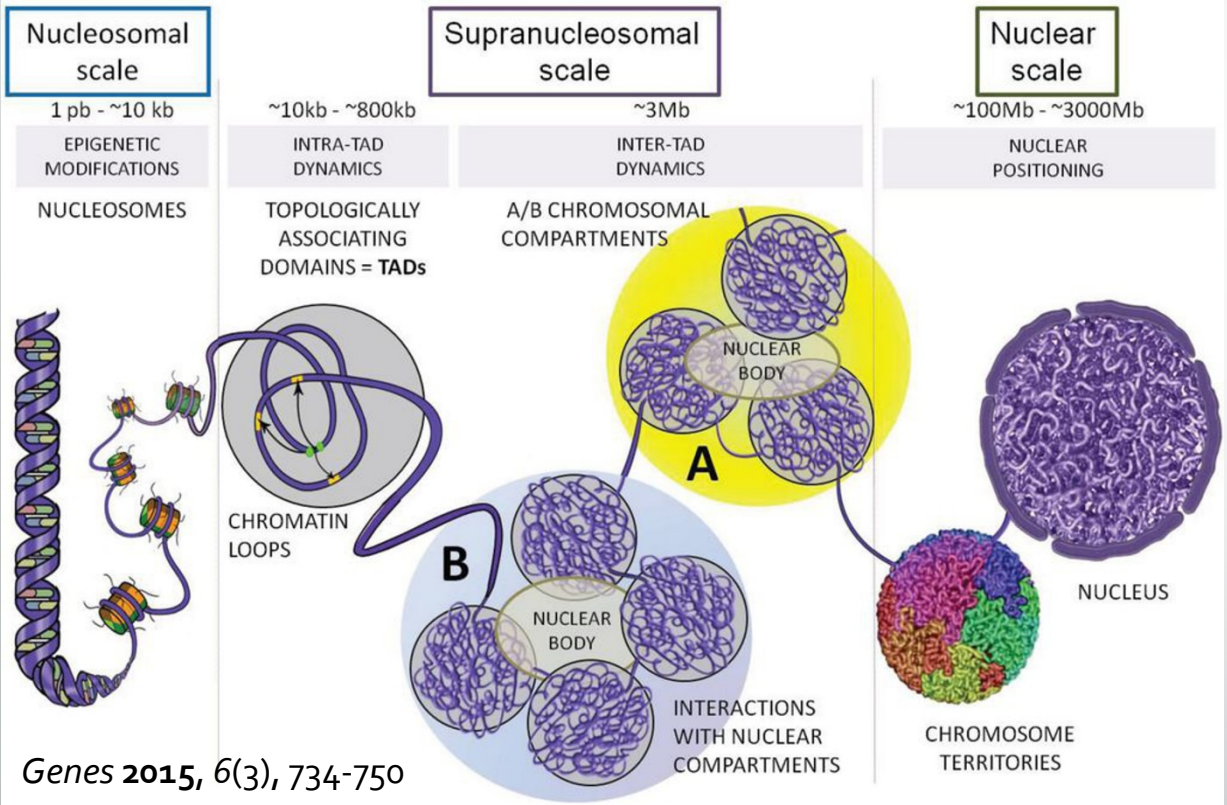
$$\text{entropy} = -\text{mean} \times \log_2(\text{mean}) - (1-\text{mean})\log_2(1-\text{mean})$$



Genome-wide MML and NME Distributions



Topologically Associating Domains

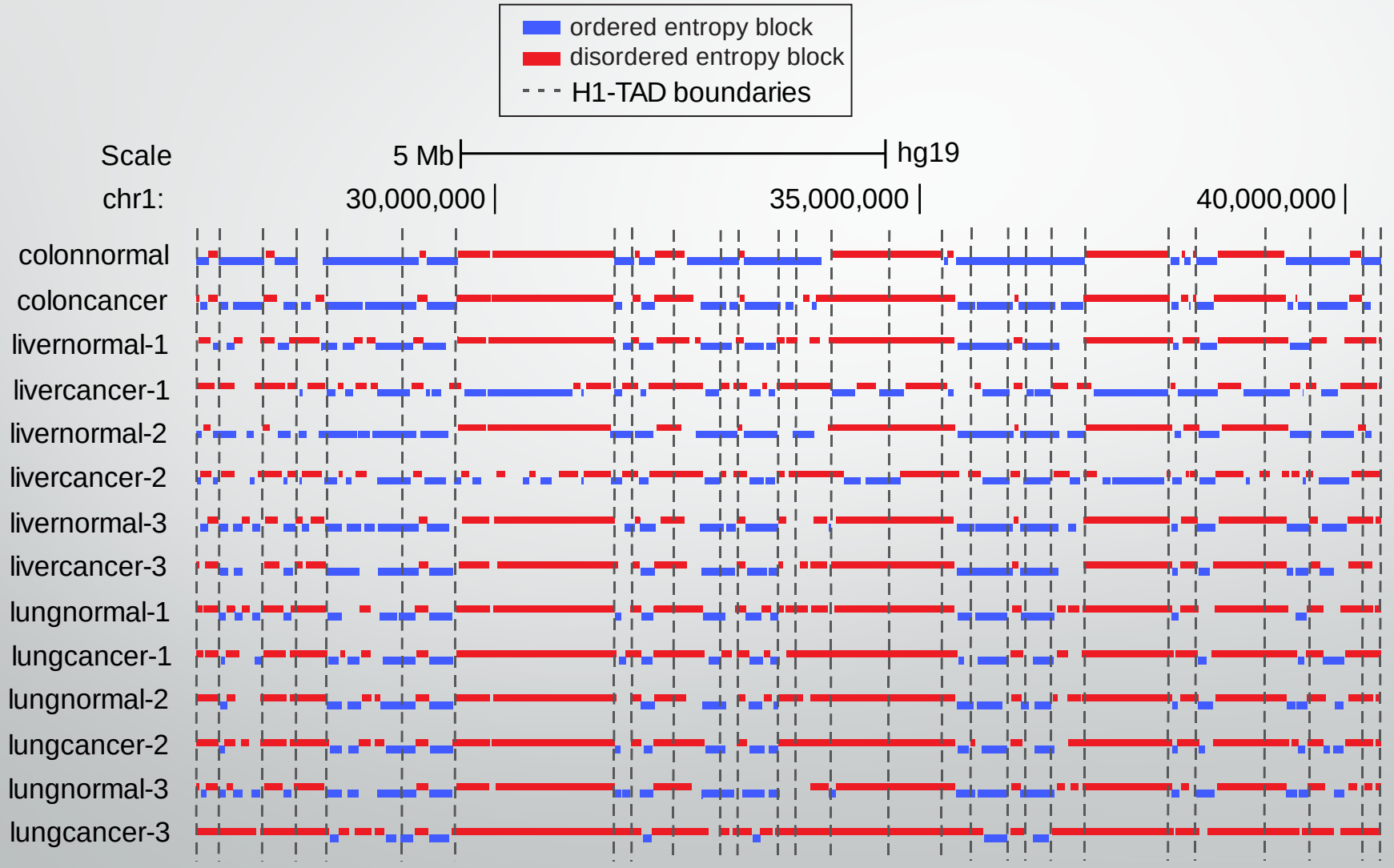


Genes **2015,** *6*(3), 734-750

- **Topologically associating domains** (TADs): highly conserved structural features of the genome across tissue types and species.
- Loci within TADs tend to interact frequently with each other.
- Less frequent interactions take place between loci within adjacent TADs.

Entropy Blocks

Large genomic regions of consistently low or high NME values.



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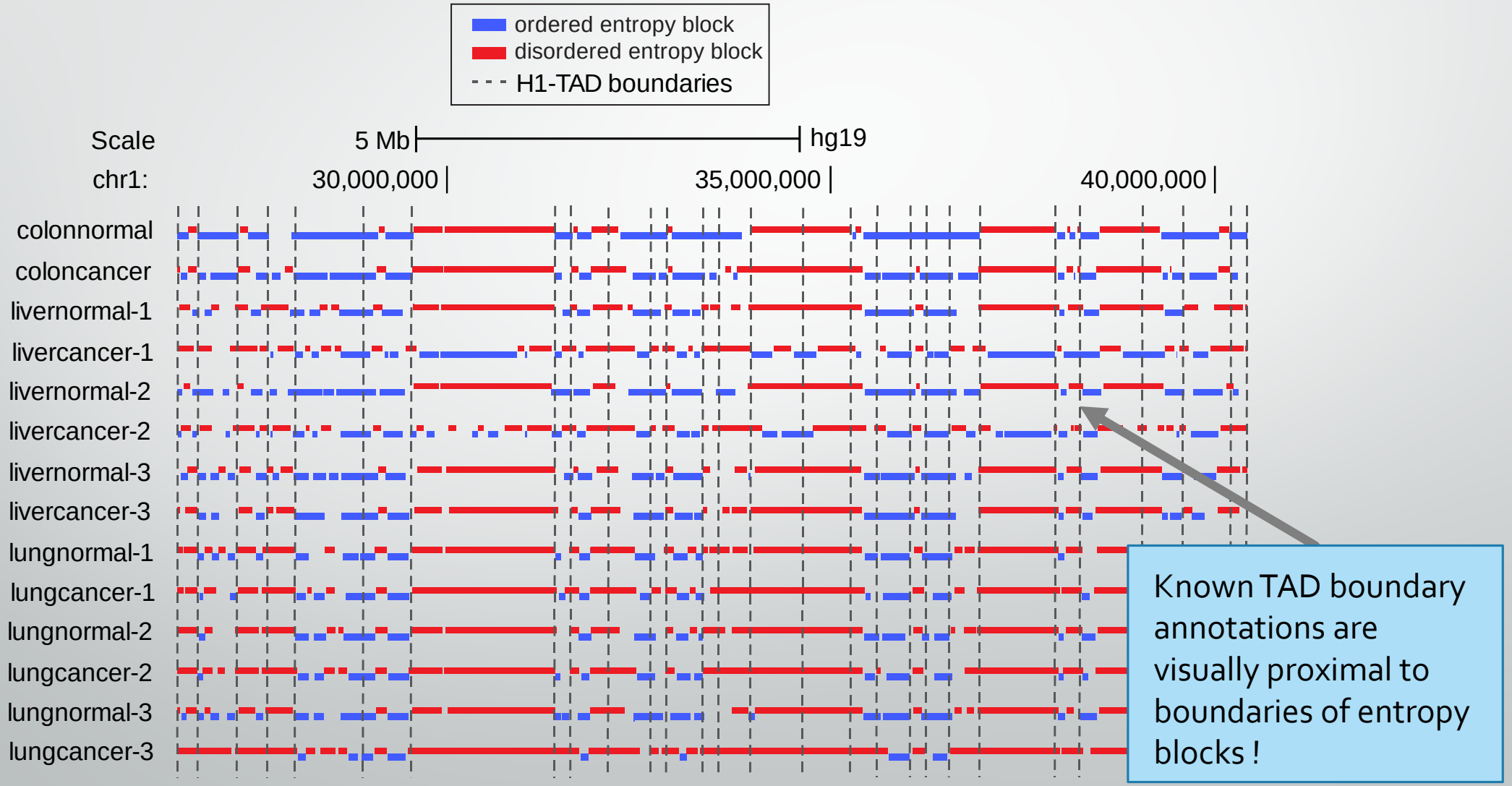
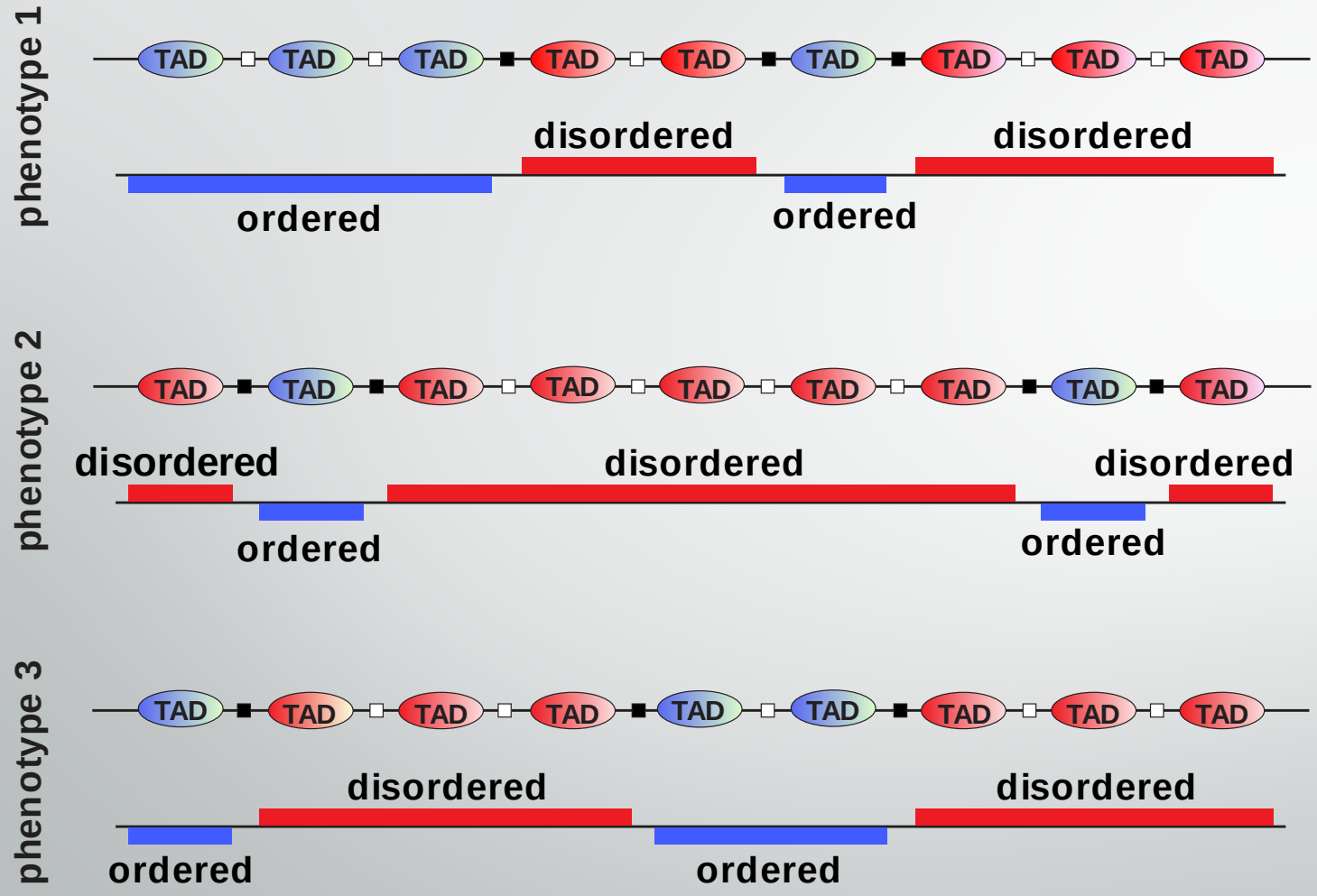
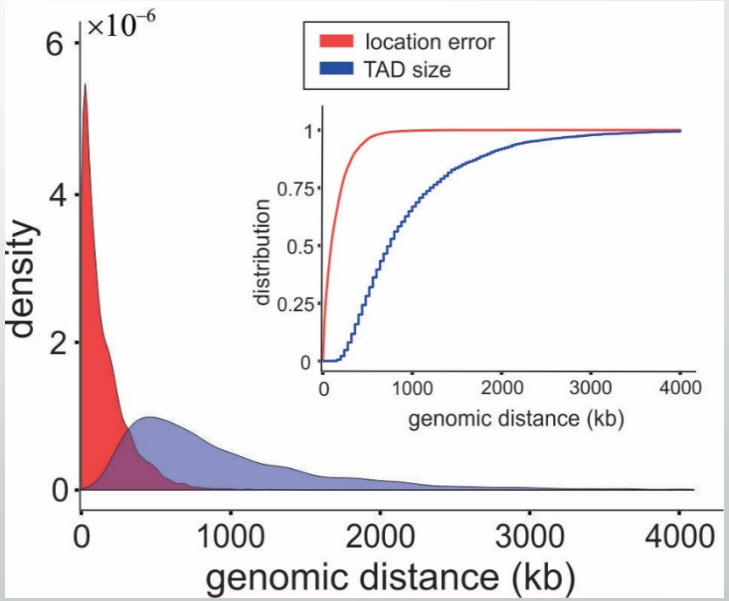


Identification of TAD boundaries

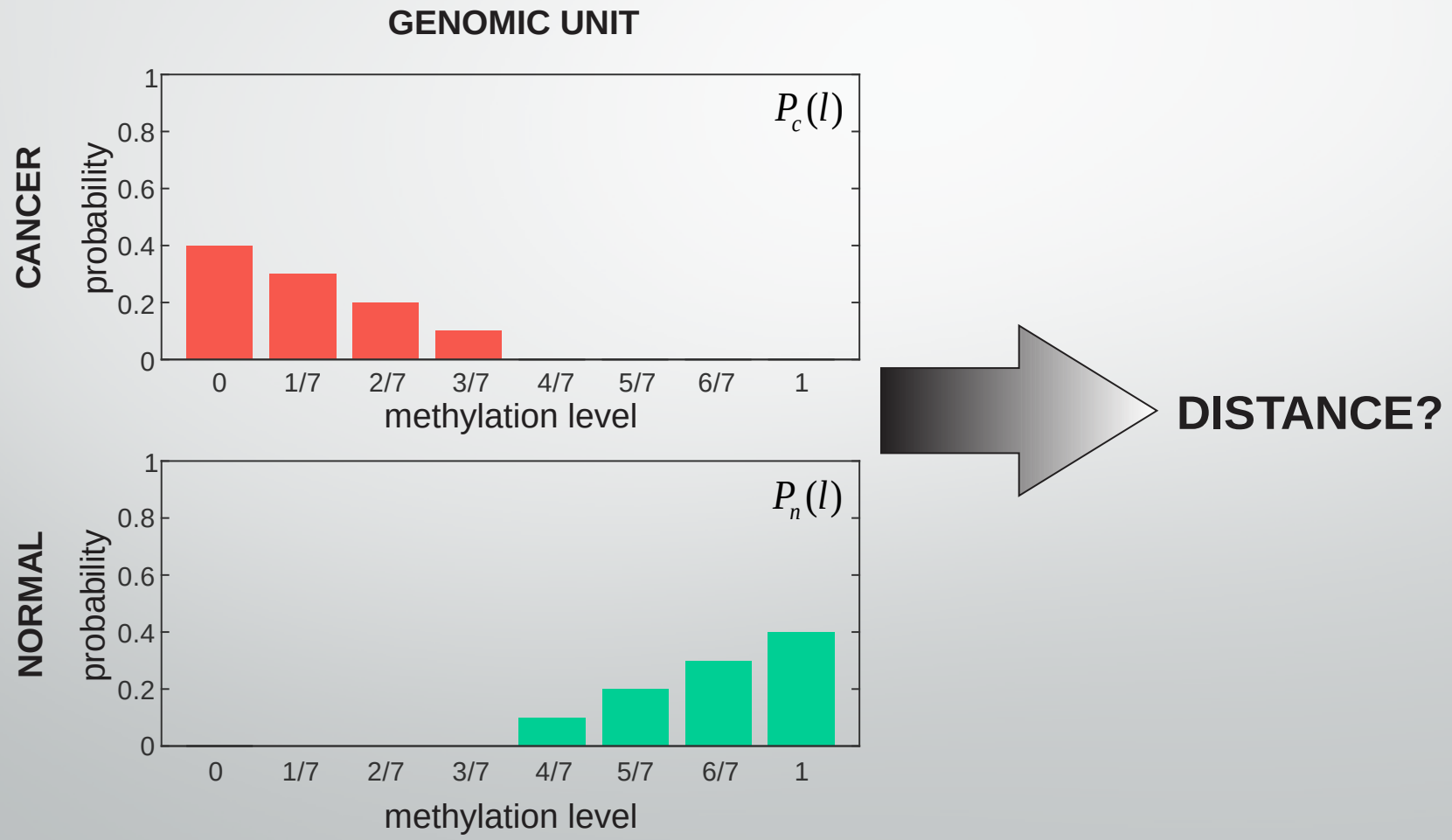


TADs are associated with consistently low or high NME values, and can be accurately identified from entropy blocks.

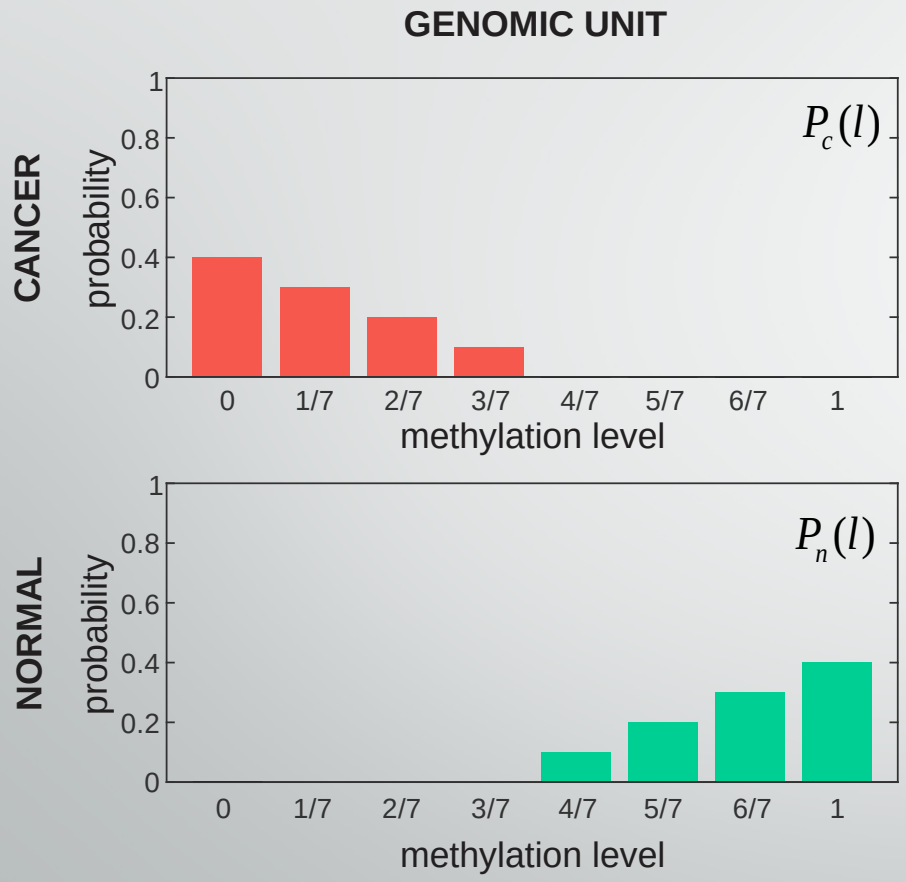


Quantifying Epigenetic Discordance

- Evaluate differences in probability distributions of methylation levels within genomic units using a distance metric.



Jensen-Shannon Distance

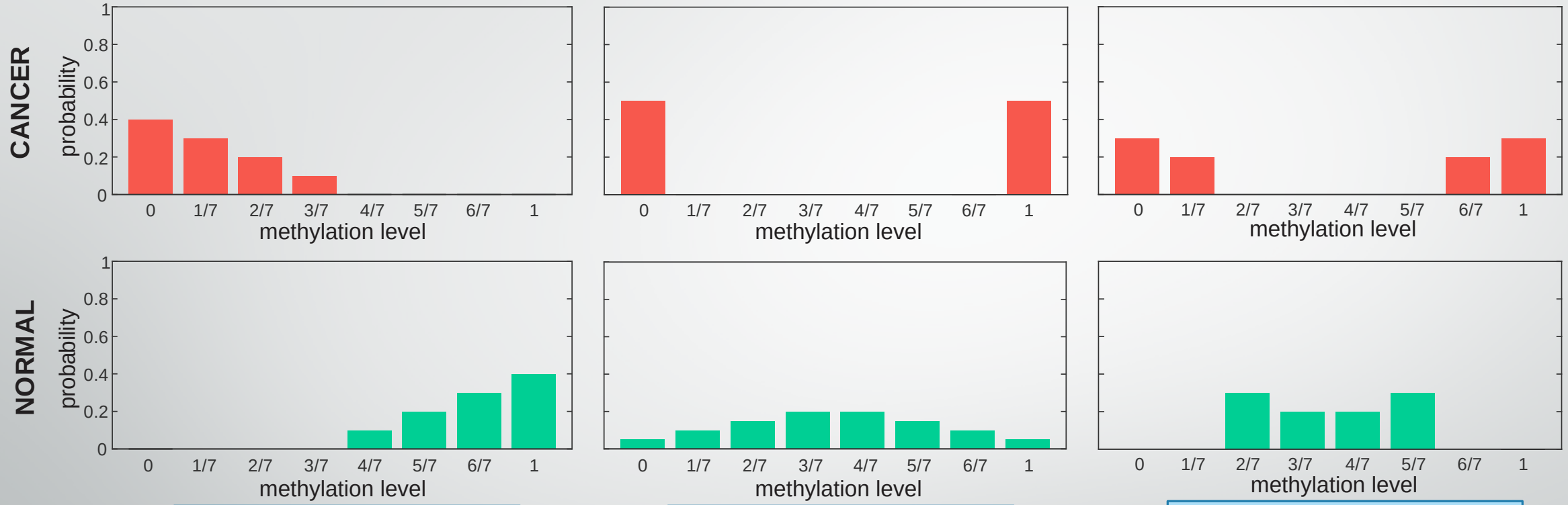


$$D_{JS} = \sqrt{\frac{1}{2}\left[D_{KL}(P_n(l), \frac{P_n(l)+P_c(l)}{2}) + D_{KL}(P_c(l), \frac{P_n(l)+P_c(l)}{2}) \right]}$$

$$D_{KL}(P,Q) = \sum_l P(l) \log_2 \left[\frac{P(l)}{Q(l)} \right]$$

$$0 \le D_{JS} \le 1$$

Jensen-Shannon Distance



JSD = 1.0
|dMML| = 0.7
|dNME| = 0.0

JSD mainly driven by difference in **MML**

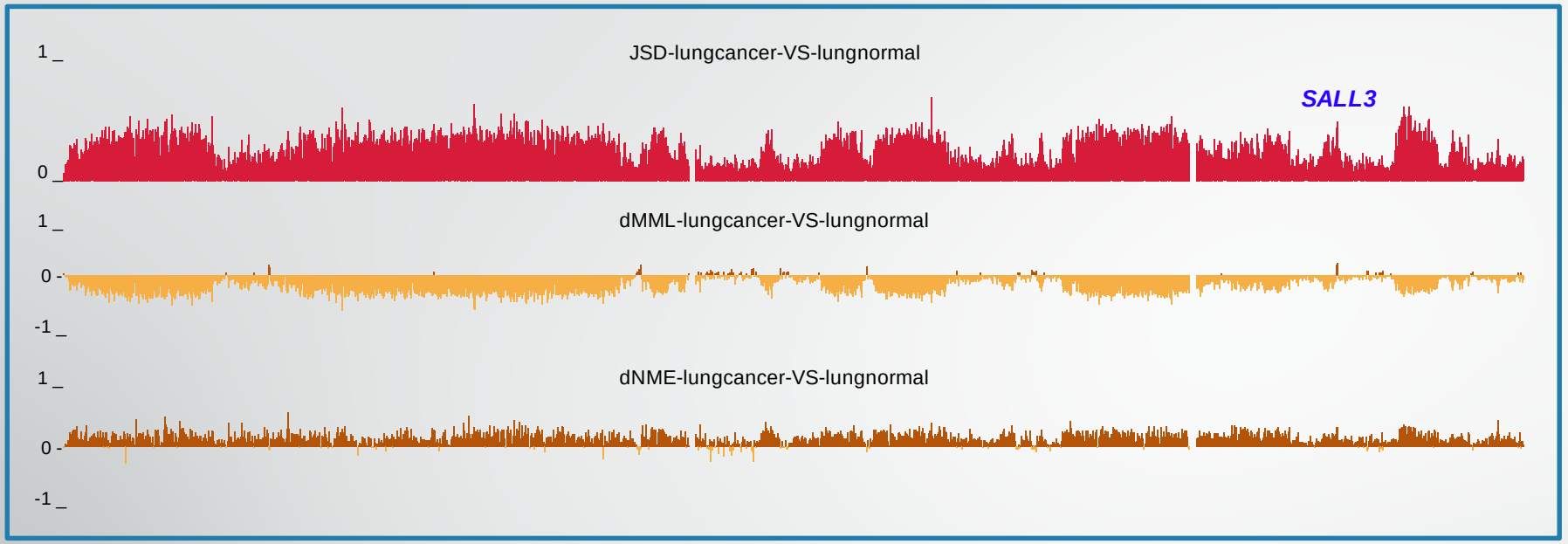
JSD = 0.9
|dMML| = 0.0
|dNME| = 0.6

JSD mainly driven by difference in **NME**

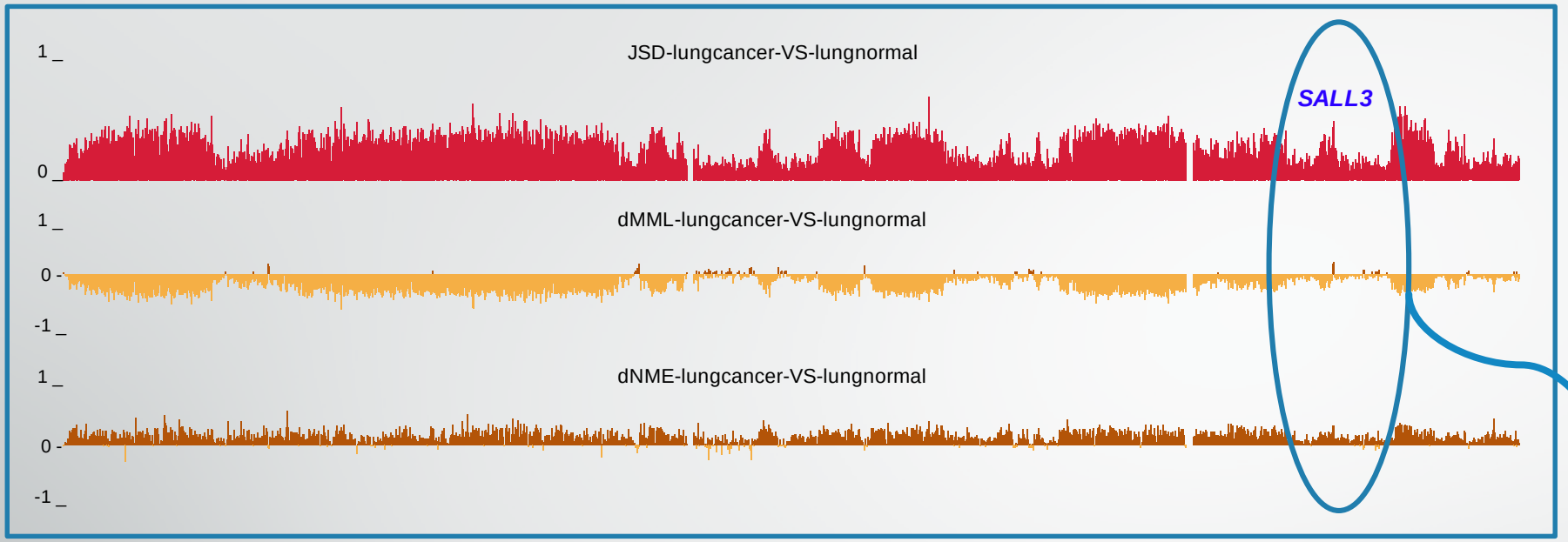
JSD = 1.0
|dMML| = 0.0
|dNME| = 0.0

JSD driven by factors **other than** MML or NME

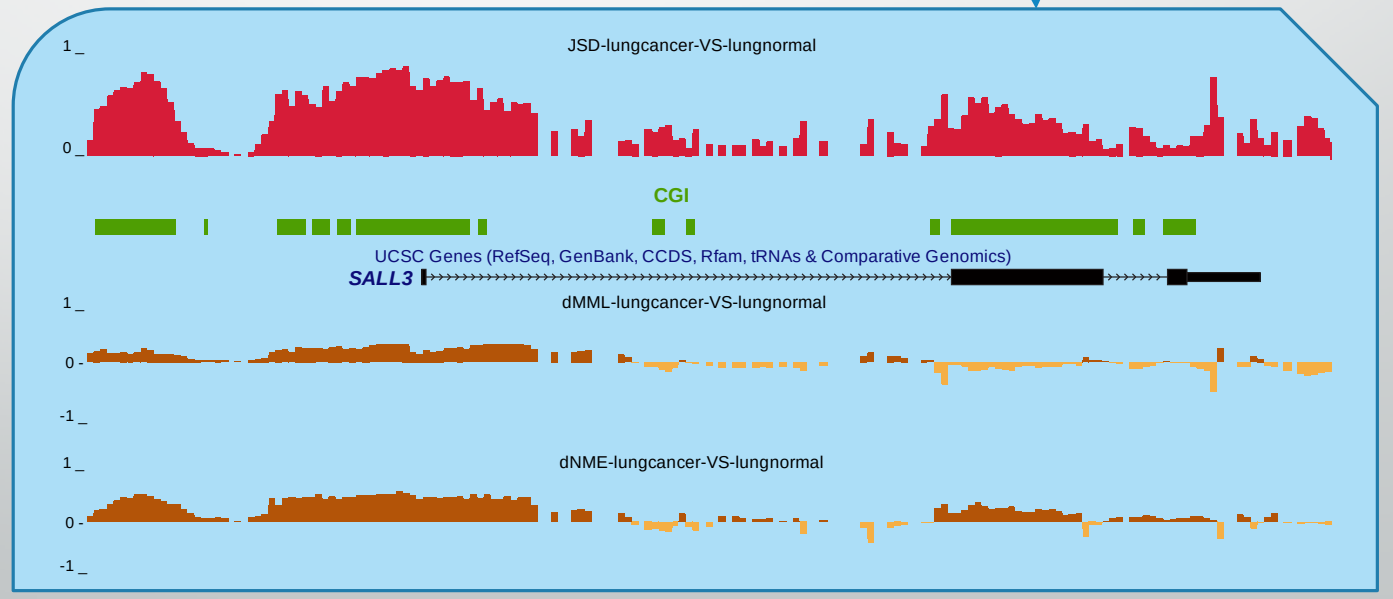
Jensen-Shannon Distance



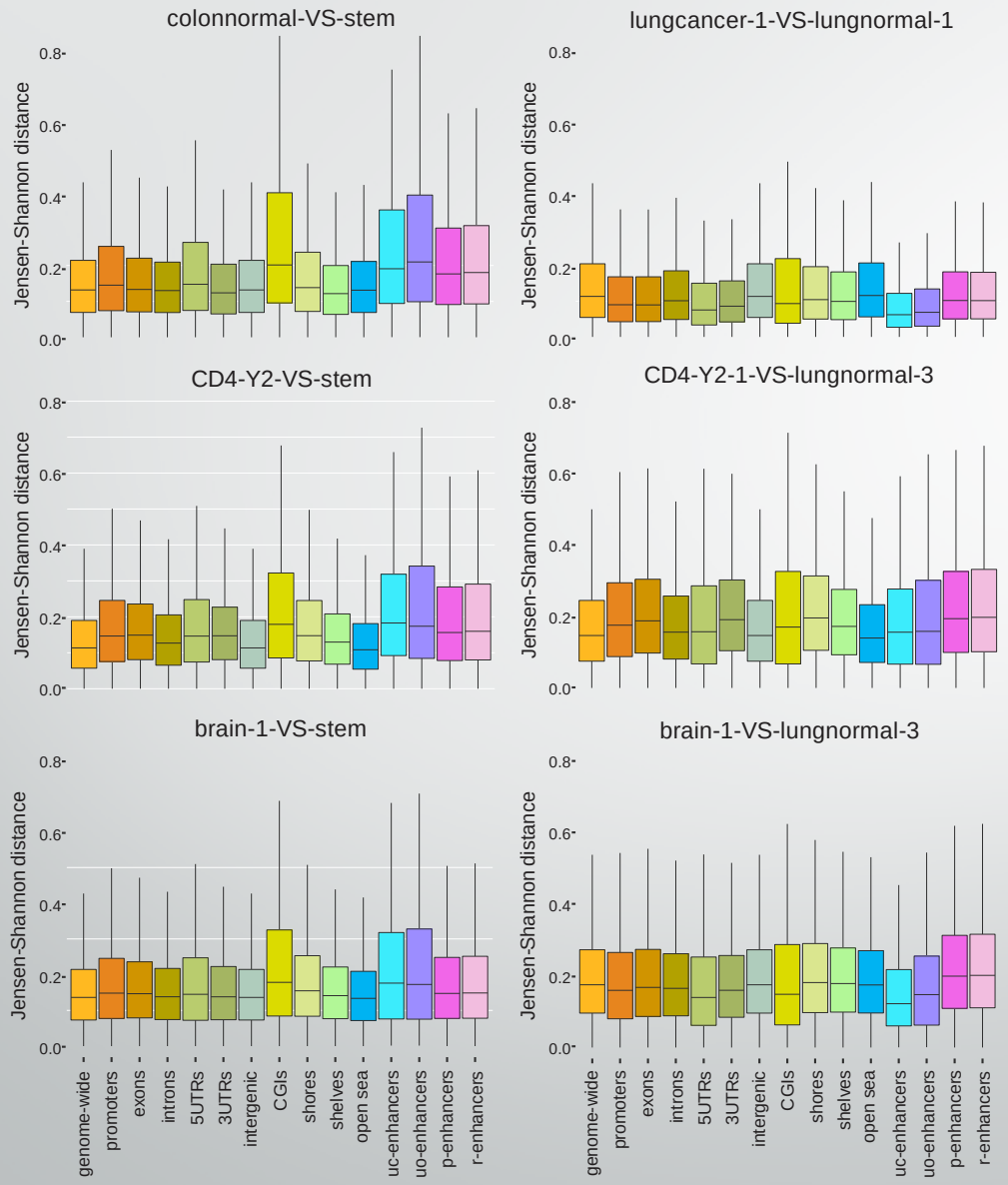
Jensen-Shannon Distance



SAL3 has been implicated in lung cancer

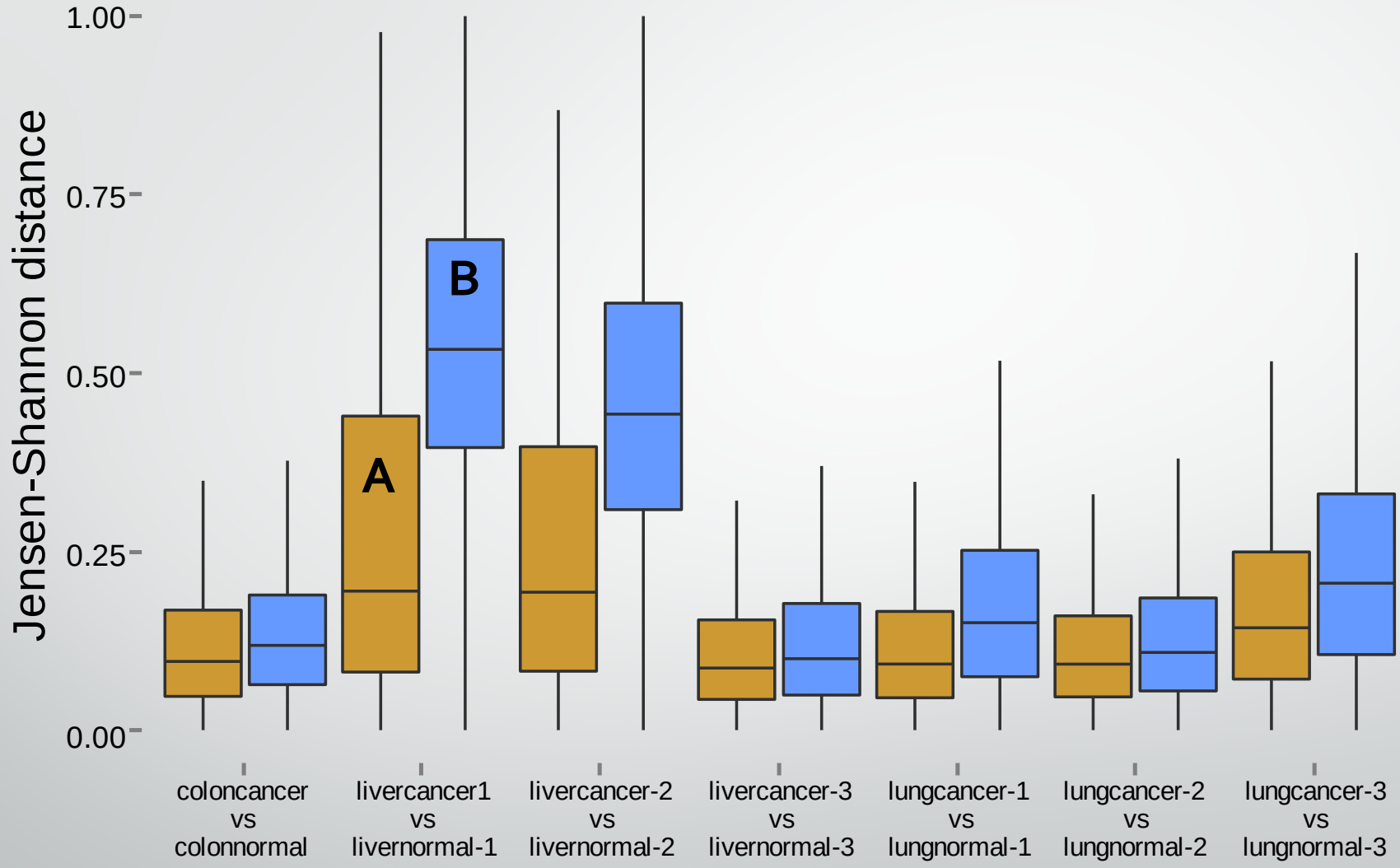


Jensen-Shannon Distance



No consistent containment of epigenetic dissimilarity within a particular genomic feature.

Jensen-Shannon Distance



Larger epigenetic discordance is observed in compartment B than in A.

Jensen-Shannon Distance

- Quantified epigenetic discordance between two samples by calculating the average of all JSD values computed genome-wide.
- Computed this measure of epigenetic discordance between 17 representative samples.
- Formed the corresponding dissimilarity matrix.
- Used multidimensional scaling to find a 2D configuration of points whose inter-point distances approximately correspond to the epigenetic dissimilarities among the samples.

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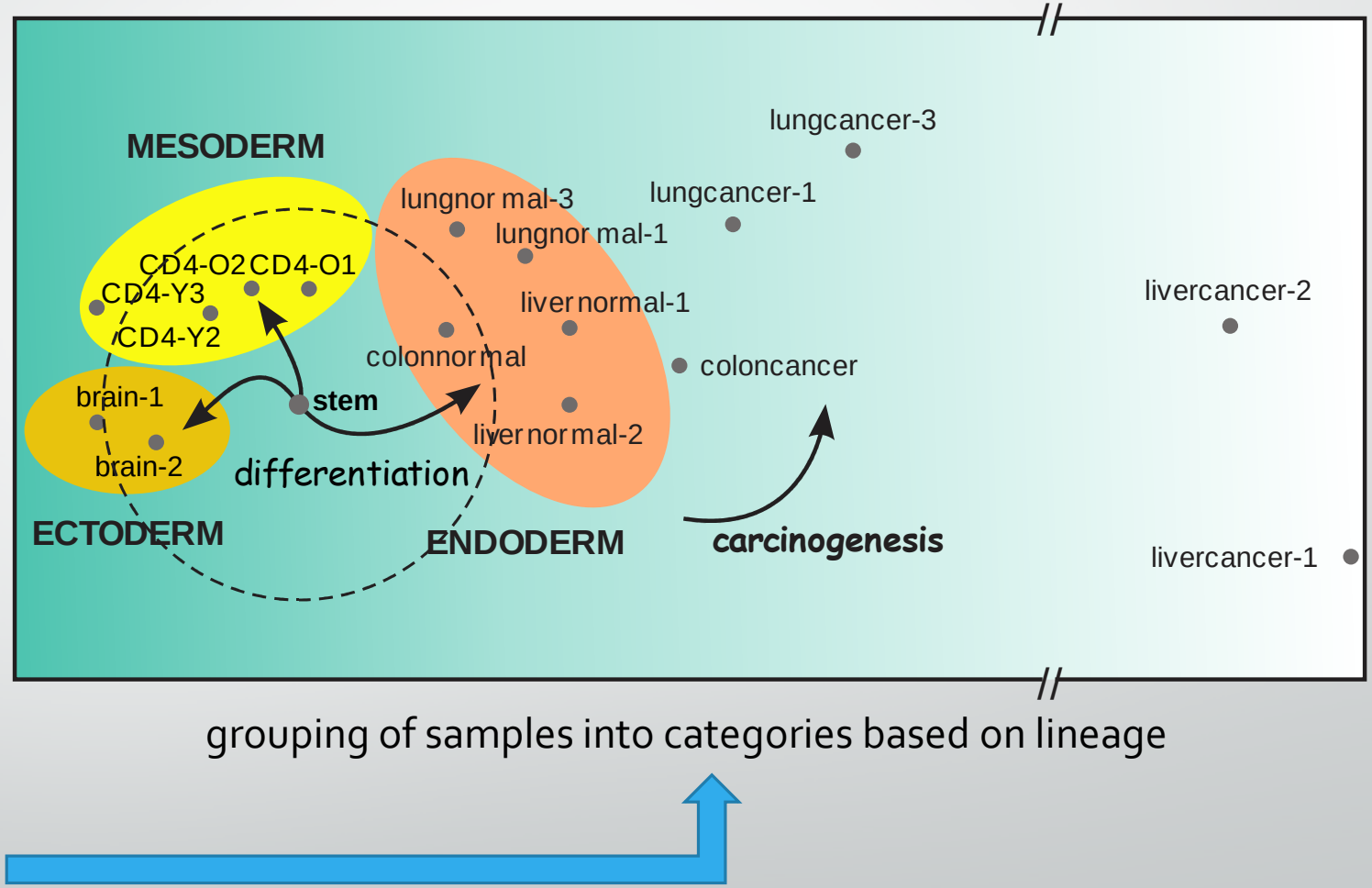


Sensitivity Analysis

- Epigenetic changes integrate environmental signals with genetic variation to modulate phenotype.
- Quantify influence of environmental exposure on methylation stochasticity.
- View environmental variability as a process that directly influences the parameters of the methylation potential energy landscape (Ising parameters).

Entropic Sensitivity Index

- Consider the case for which the Ising parameters $\boldsymbol{\theta}$ fluctuate around their true values by a random amount $G \times \boldsymbol{\theta}$, where G is a zero-mean normal distribution with standard deviation σ.
- Can show that

$$\sigma_h \simeq \eta \times \sigma$$

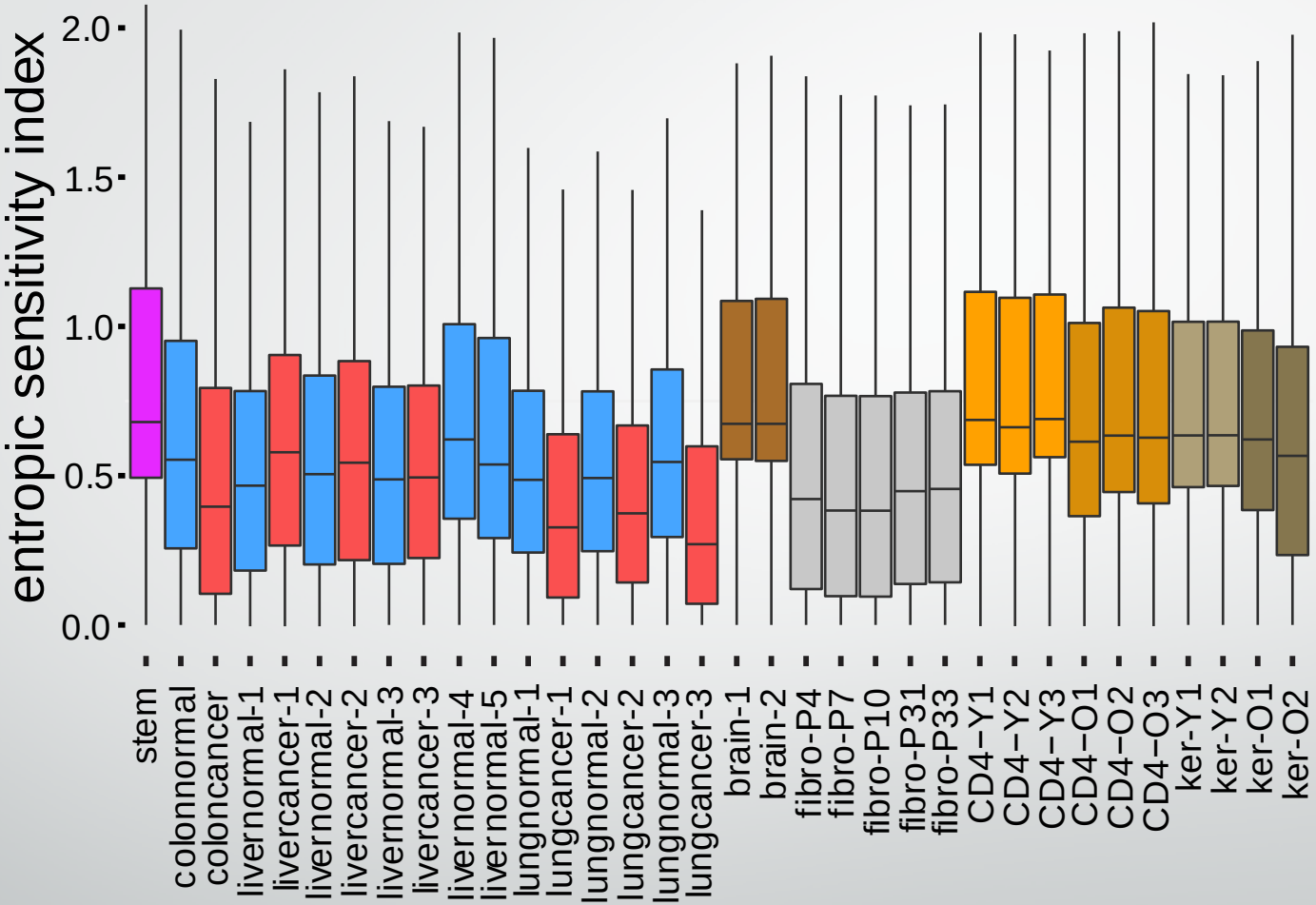
variation in entropy (NME)

environmental variation

$$\eta = \left| \frac{\partial h(g)}{\partial g} \right|_{g=0}$$

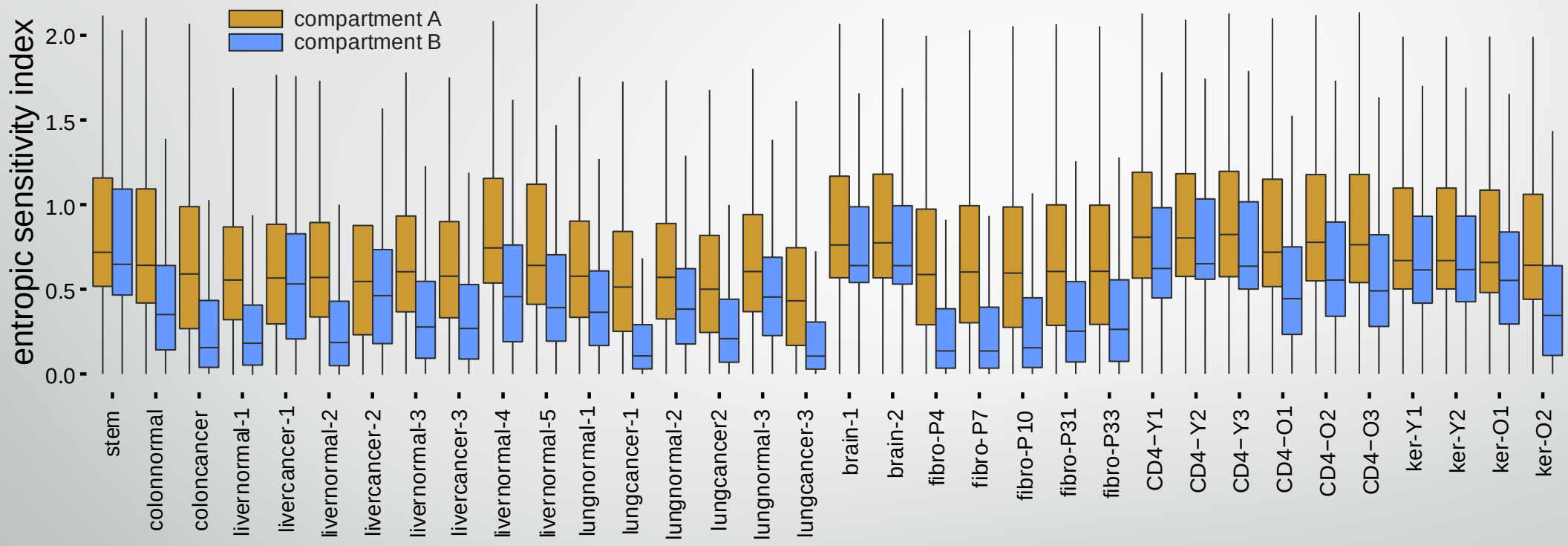
Entropic sensitivity index (ESI)

Sensitivity Analysis



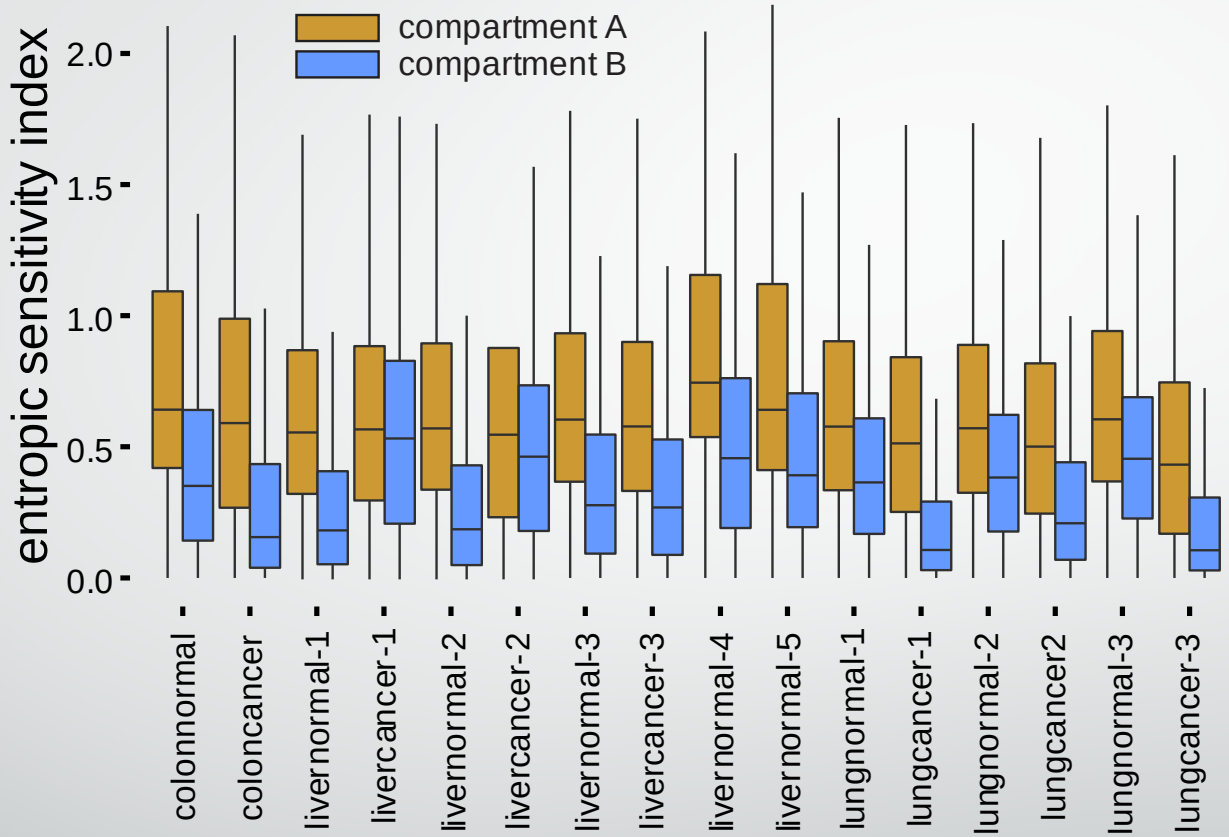
Globally observed differences in entropic sensitivity among tissues.

Sensitivity Analysis



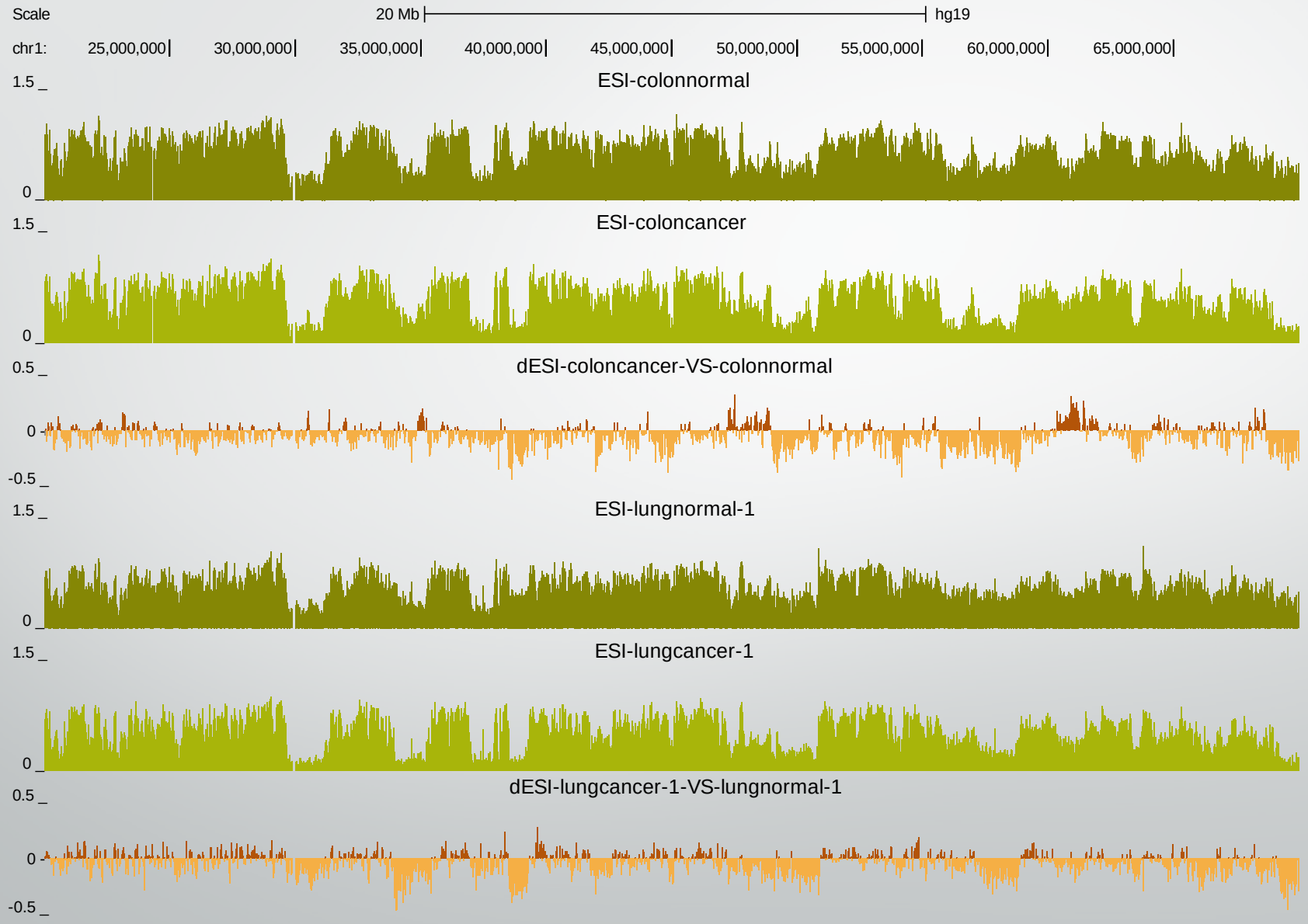
Entropic sensitivity within compartment A is higher than in compartment B.

Sensitivity Analysis



Observed differences between normal and cancer are largely confined to compartment B.

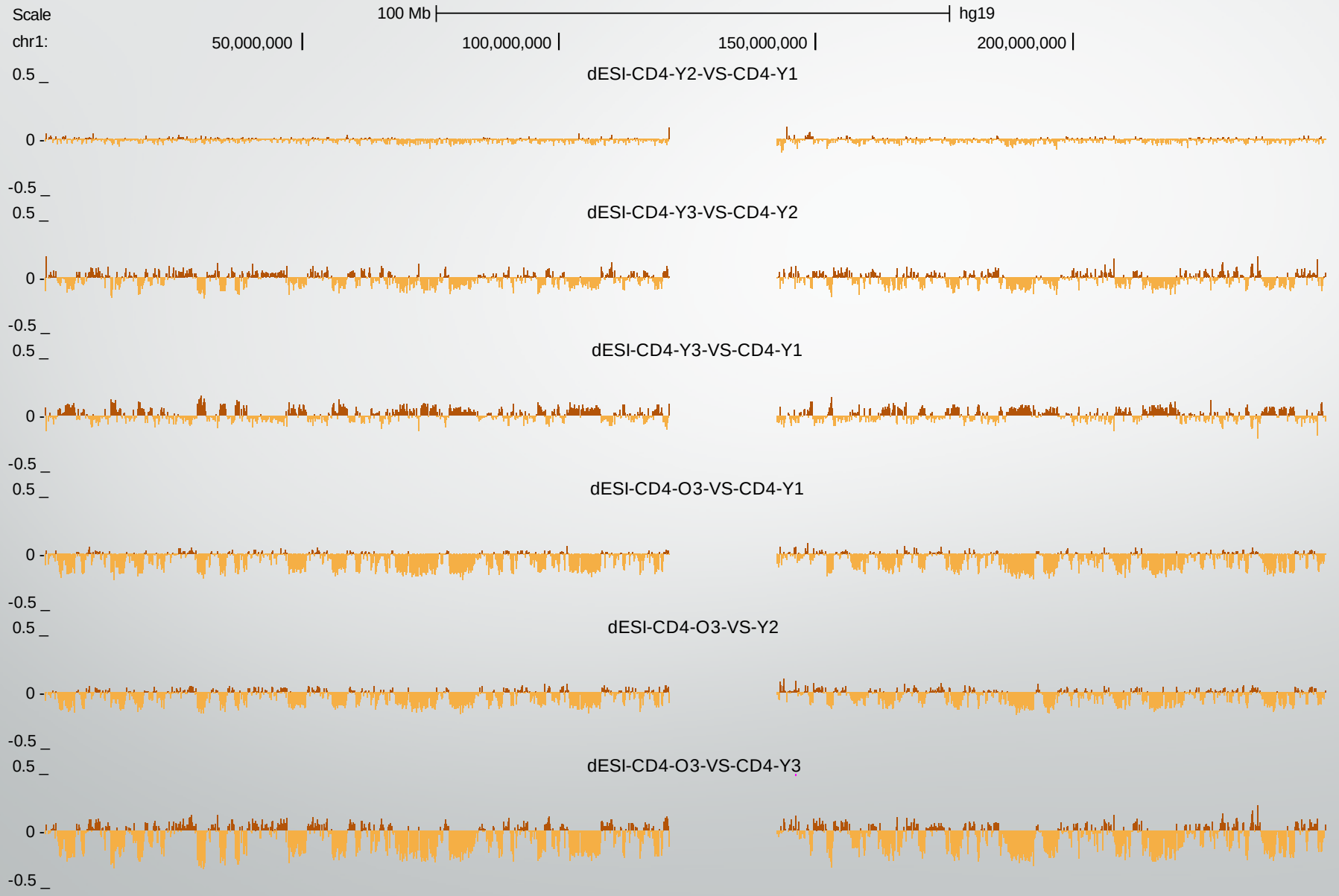
Sensitivity Analysis (Normal-Cancer)



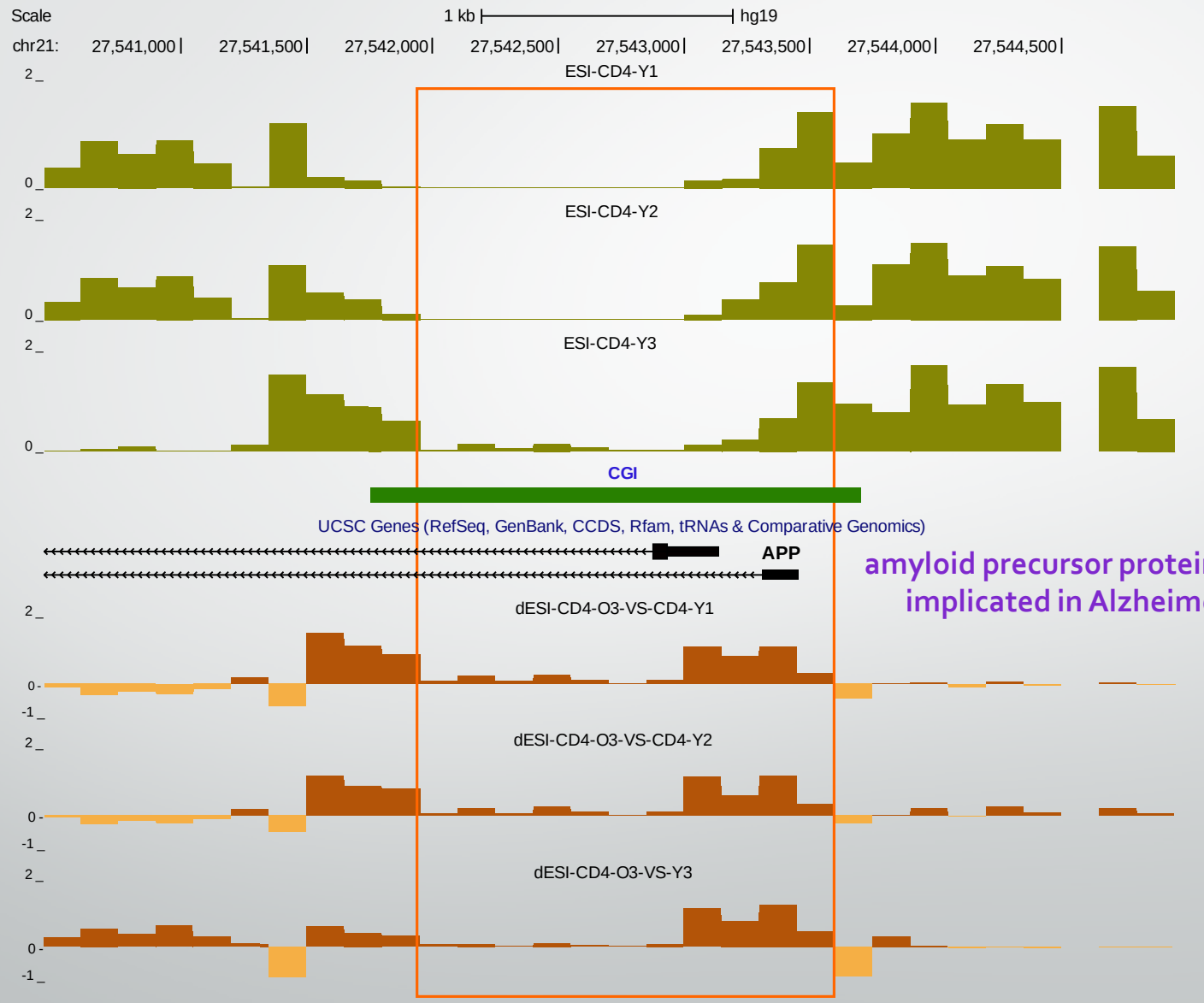
Sensitivity Analysis (Normal-Cancer)

polycomb target gene proposed as a candidate gene for type 2 diabetes

Sensitivity Analysis (Young-Old)



Sensitivity Analysis (Young-Old)



amyloid precursor protein gene implicated in Alzheimer's

Conclusion

- An information-theoretic approach to epigenomics based on the Ising model provides a formal foundation to methylation analysis.
- Yields fundamental insights into epigenetic behavior.
- Demonstrates a relationship between
  - chromatin structure
  - methylation channels
  - entropic sensitivity
- This may maximize an organism's efficiency in storing epigenetic information and help explain developmental plasticity.

Conclusion

- Pluripotent stem cells require relatively **high energy** to maintain **high capacity** methylation channels within a portion of the genome, achieving **reduced methylation stochasticity**.
- Regions characterized by **increased entropic sensitivity** are associated with **highly deformable potential energy landscapes**, which may correspond to differentiation branch points.
- After differentiation, some large genomic domains, such as regions associated with pluripotency, need not maintain high channel capacities and energy consumption
  - their sequestration providing **increased energy efficiency** with the cost of **high epigenetic stochasticity** and **reduced responsiveness**.